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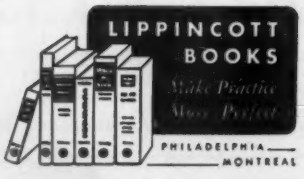
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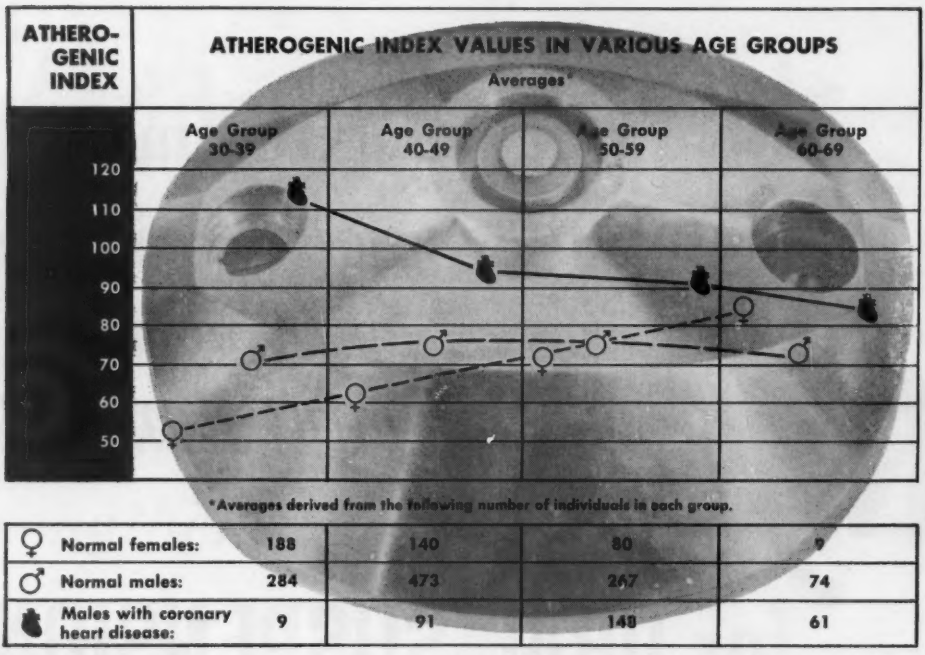


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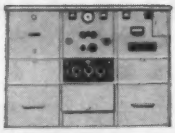
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1. *Tittle, C.R.: The Effects of 3,5,3' L-triiodothyronine in Patients with Metabolic Insufficiency, J.A.M.A. 162:271 (Sept. 22) 1956.*

Cytomel*

5 mcg. and 25 mcg. (scored) tablets

the new agent to improve metabolic function

More than 200 published reports now describe the action of L-triiodothyronine ('Cytomel'). Its clinical usefulness has been confirmed in treating conditions of decreased metabolic function.

*Trademark for liothyronine (L-triiodothyronine), S.K.F.

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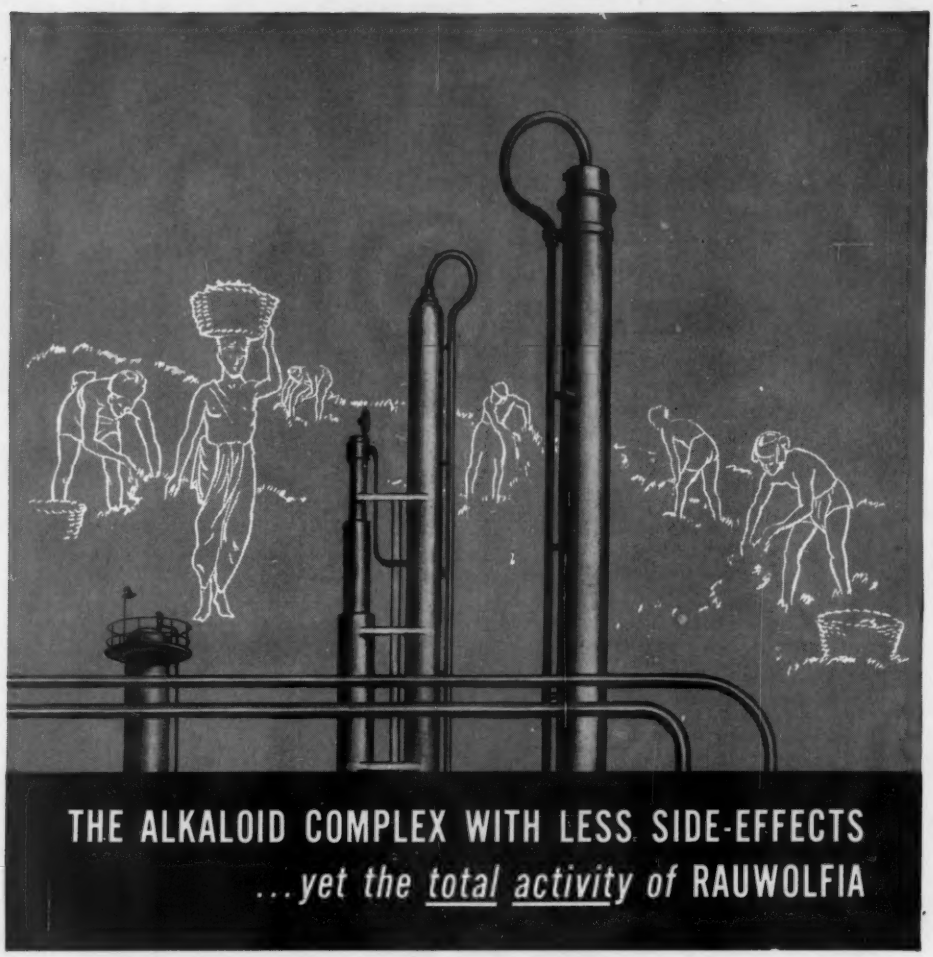
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Rautensin (the alseroxylon fraction complex of Rauwolfia) contains both rescinnamine and reserpine, together with the other valuable alkaloids.

Produces a gradual and sustained drop in blood pressure.

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The alseroxylon fraction complex of Rauwolfia was found less prone to cause mental depression.[1]

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1. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96: 530, 1955

Rautensin®

Each tablet contains 2 mg. *purified* Rauwolfia serpentina alkaloids (alseroxylon fraction)

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it symbolizes an unsurpassed preparation for thyroid therapy


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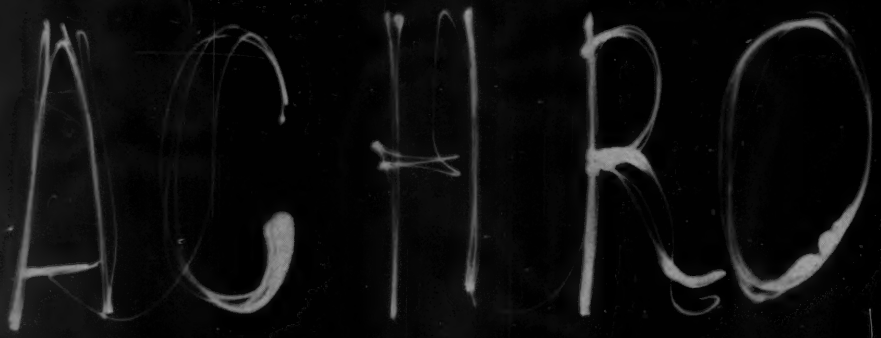
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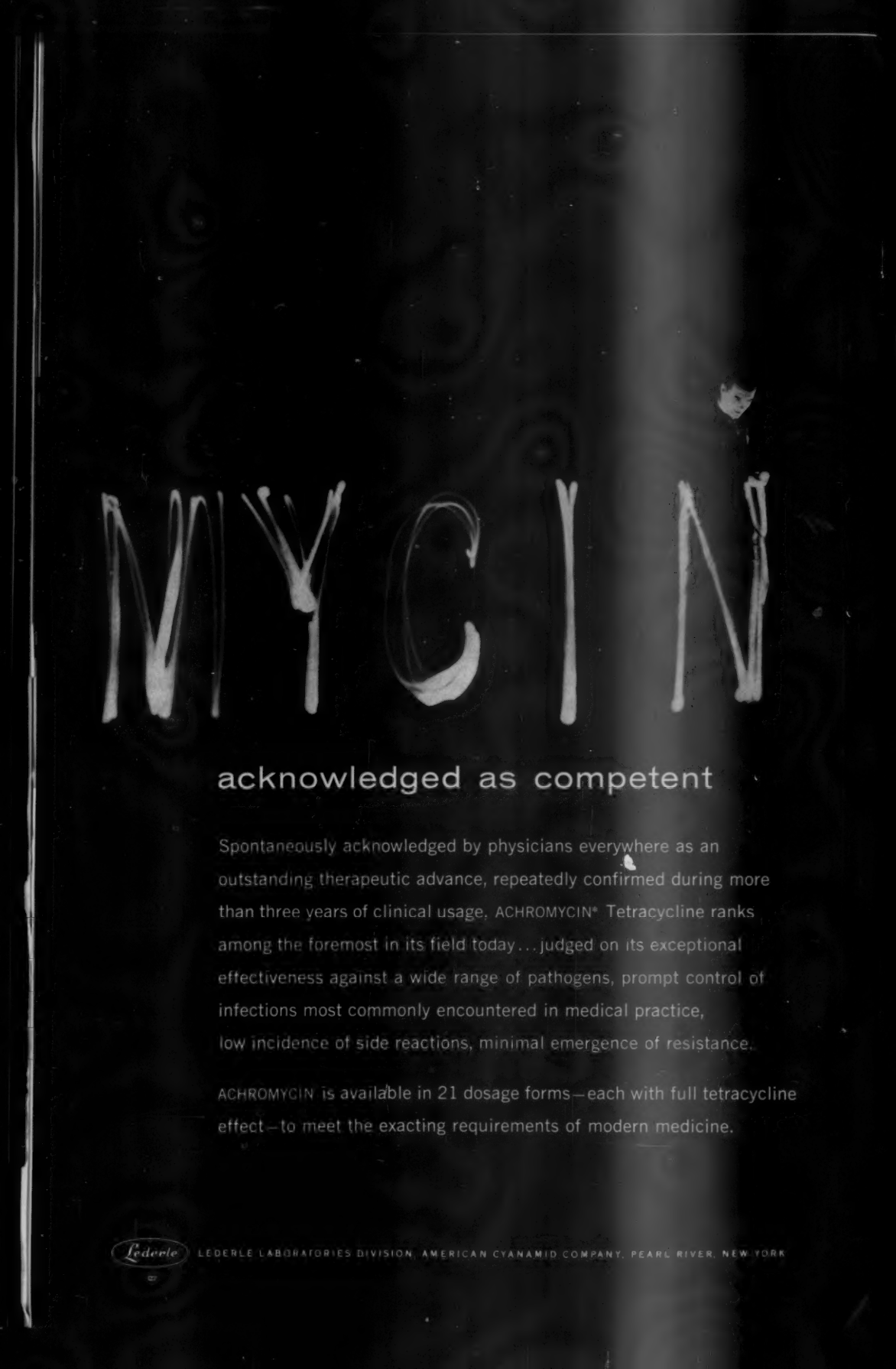


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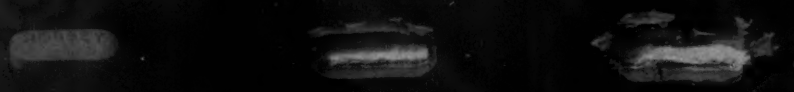
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2-STAGE DISINTEGRATION . . .

The outer layer of Buffered Pabirin Tablets quickly releases aluminum hydroxide for buffering action. PABA to potentiate acetylsalicylic acid and therapeutic doses of ascorbic acid to offset depletion are also in the outer layer.

The inner core of Buffered Pabirin Tablets containing acetylsalicylic acid alone begins to expand after the buffering action has started.

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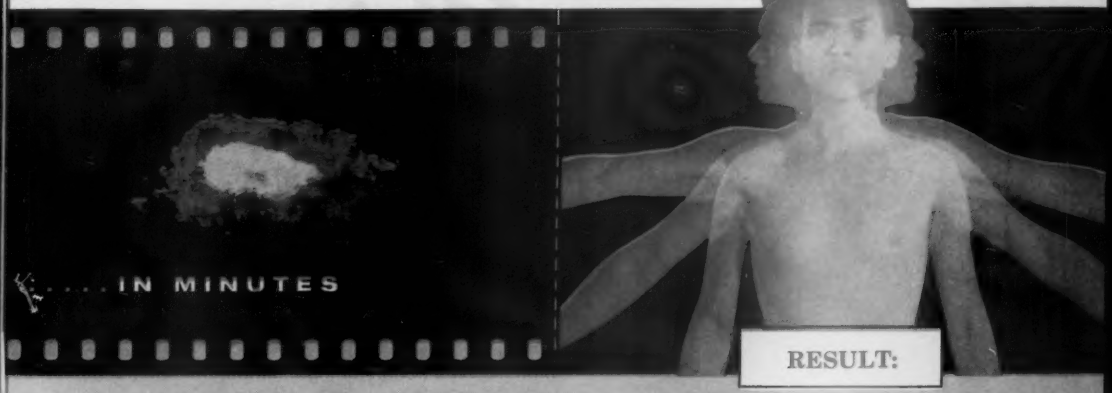
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☆ buffered for superior gastric tolerance

☆ buffered for faster pain relief



The inner core then disintegrates rapidly and permits fast absorption of the acetyl salicylic acid.

Buffered Pabirin AC Tablets release, in addition, hydrocortisone from the core.

RESULT:

- increased range of motion
- faster pain relief
- superior gastric tolerance

for most rheumatoid arthritics

Buffered Pabirin® TABLETS

300 mg.	Acetylsalicylic acid (5 gr.)	300 mg.
300 mg.	Para-aminobenzoic acid (5 gr.)	300 mg.
50 mg.	Ascorbic acid	50 mg.
100 mg.	Dried aluminum hydroxide gel	100 mg.

Dosage: Two or three tablets 3 or 4 times daily. In rheumatic fever three to five tablets 4 or 5 times daily.

for resistant rheumatics

Buffered Pabirin® AC TABLETS

	Hydrocortisone	2.5 mg.
300 mg.	Acetylsalicylic acid (5 gr.)	300 mg.
300 mg.	Para-aminobenzoic acid (5 gr.)	300 mg.
50 mg.	Ascorbic acid	50 mg.
100 mg.	Dried aluminum hydroxide gel	100 mg.

Dosage: Initially, one or two tablets 4 times daily, after meals and on retiring. Reduction of dosage should be gradual; never stopped abruptly.

Combined for a new resistant

new

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METICORTEN (PREDNISONE) PLUS CHLOR-TRIMETON WITH ASCORBIC ACID

For prompt and effective relief, especially in many resistant allergic disorders, METRETON affords the benefits of two established agents with unexcelled anti-inflammatory, anti-allergic and antipruritic effectiveness. ***supported by essential vitamin C***—for stress support and for postulated effect on prolonging steroid action ***no better corticosteroid***—original brand of prednisone...minimal electrolyte effects—METICORTEN ***no better antihistamine***—unexcelled in potency and freedom from side effects—CHLOR-TRIMETON effective against hay fever, pollen asthma, perennial rhinitis, acute and chronic urticaria, angioneurotic edema, drug reactions, inflammatory and allergic eye disorders, pruritic and contact dermatoses.

formula: Each tablet of METRETON provides 2.5 mg. of METICORTEN (prednisone), 2 mg. of CHLOR-TRIMETON maleate (chlorprophenpyridamine maleate), and 75 mg. ascorbic acid.

supplied: METRETON Tablets, bottles of 30 and 100.

frontal attack

allergies

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quickly clears nasal passages • avoids rebound engorgement and sympathomimetic side effects • safe even for cardiacs, hypertensives, children, pregnant patients •

Composition: Contains 2 mg. (0.2%) METICORTELONE acetate (prednisolone acetate) and 3 mg. (0.3%) of CHLOR-TRIMETON gluconate (chlorprophenpyridamine gluconate) in each cc.

Packaging: 15 cc. plastic "squeeze" bottle, box of 1.

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MT-J-575



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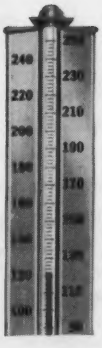


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. . . from incapacitating hypertension to a life of usefulness.

Case History:[1] A.B., 42-year-old hospitalized patient with severe hypertension and early heart failure. Blood pressure prior to treatment was 240/160 mm. Hg. ANSOLYSEN was administered orally t.i.d. The dose was adjusted to the patient's requirements. Blood pressure was reduced to, and stabilized at, an average level of 150/105 mm. Hg. There was marked symptomatic improvement, and the patient was able to return to work.

1. Case history on file in Medical Department of Wyeth Laboratories.



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TARTRATE Pentolinium Tartrate

Lowers Blood Pressure

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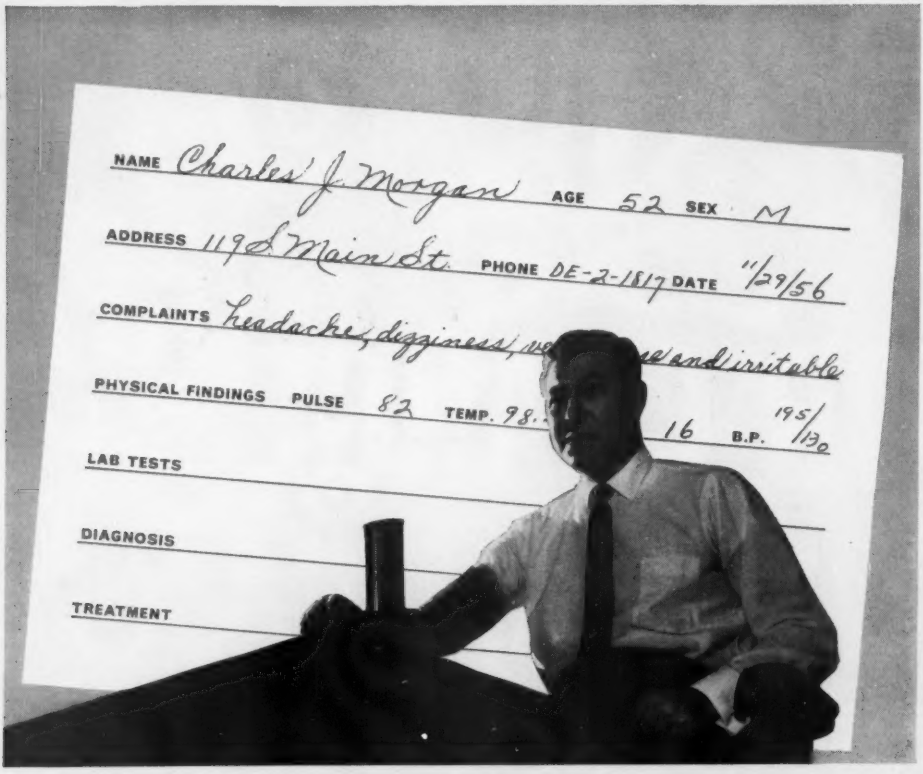
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If parenteral digitalization is imperative, or when a change in route of administration is required, DIGITALINE NATIVELLE eliminates the possible source of error associated with complex recalculation of dosage. And uncomfortable toxic symptoms occurring with dosage revision are also avoided, because DIGITALINE NATIVELLE requires only one change—to the dosage form of choice: oral, intramuscular or intravenous. All forms provide identical dosage schedules, complete absorption, equal rate of onset.

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Safety is a distinguishing feature of *Rauvera*, a potent antihypertensive agent with safeguards inherent in the purified mixed alkaloid fractions, alseroxylon (1 mg. per tablet) and alkavervir (3 mg. per tablet). The risks of depression, postural hypotension or reduction of blood pressure to undesirable levels are virtually absent with *Rauvera*. Patients can be started routinely on *Rauvera*, and therapy can be continued over long periods of time.

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The patients' electrocardiogram (or other cardiovascular event) is seen on the screen of the viewing unit the instant it occurs, in the form of a bright yellow fluorescent image of exceptional sharpness and definition, and with a *four seconds* duration. The user has *precise* control of sweep speeds of 25, 50 and 100 mm/sec. Complete and instantaneous lead selection may be made. An illuminated reference scale on the screen provides for rapid estimation of ECG complexes and heart rate.

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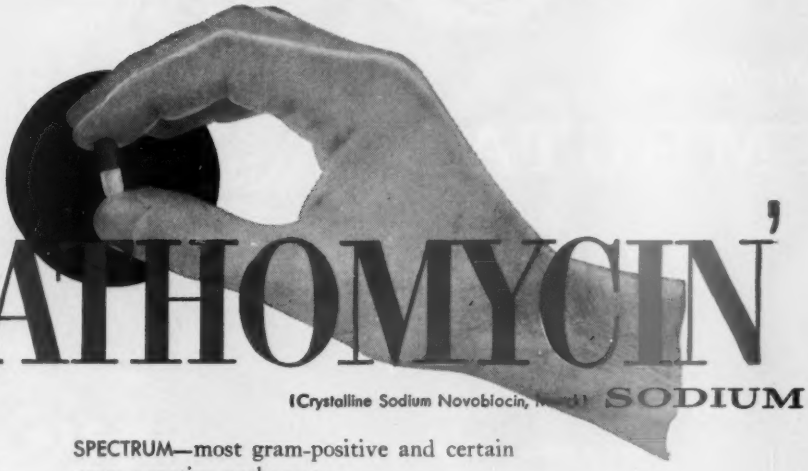
An efficient antacid suspension of magnesium-aluminum hydroxide gel; tablets, 0.4 Gm.

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PROVED EFFECTIVE AGAINST
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'CATHOMYCIN'

(Crystalline Sodium Novobiocin, [illegible]) SODIUM

SPECTRUM—most gram-positive and certain gram-negative pathogens.

ACTION—bactericidal in optimum concentration even to resistant strains.

TOXICITY—generally well tolerated. This is more fully discussed in the package insert.

ABSORPTION—oral administration produces high and easily-maintained blood levels.

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DOSAGE—four capsules (one gram) initially and then two capsules (500 mg.) twice daily.

SUPPLIED—Two capsules (500 mg.) twice daily or one capsule (250 mg.) four times a day.

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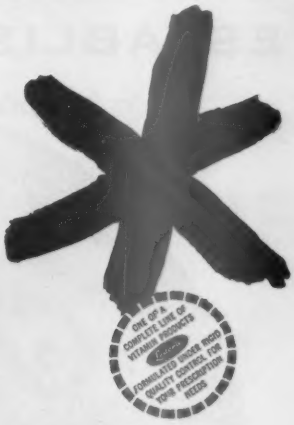
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Riboflavin (B_2)	10 mg.
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Pyridoxine HCl (B_6)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Folic Acid	3 mg.
Vitamin B_{12}	15 mcgm.

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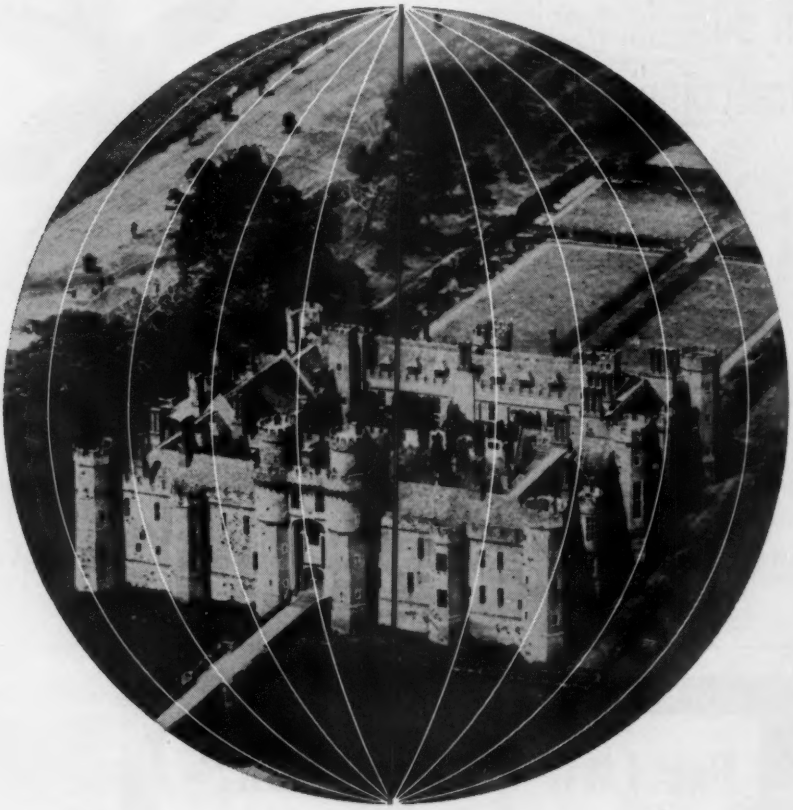
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penicillin with a surety factor

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PATIENT APPRECIATION one capsule once-a-day.



PREDICTABLE WEIGHT LOSS Rx Biphetamine capsules containing a mixture of equal parts of amphetamine and dextro amphetamine in the form of a resin complex. Three strengths—Biphetamine 20 mg., 12½ mg., 7½ mg.



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Quercetin	15 mg.
Ascorbic acid	25 mg.
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Suggested dosage: One tablet q.i.d.
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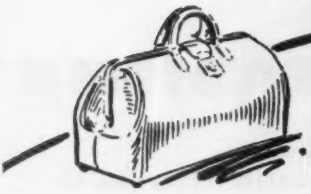
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Dilaudid—a powerful analgesic—dose, 1/32 grain to 1/20 grain.
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A new antibacterial

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plus a high degree of safety

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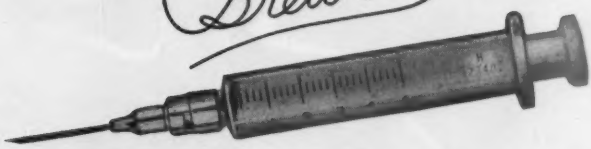
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FIRST *INJECTABLE QUINIDINE COMMERCIALLY AVAILABLE IN AMERICA*

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For those cases of auricular fibrillation and paroxysmal tachycardia where QUINIDINE is indicated and cannot be given, or is not effective, orally—

Administration: **INTRAMUSCULARLY or if necessary INTRAVENOUSLY**

Available: **Quinidine Hydrochloride Injectable (0.6 Gm.) in 5 cc. ampul**
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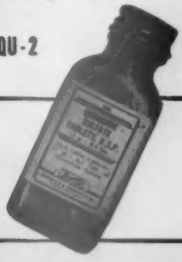
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2. Sagall, E. I.; Horn, C. D.; and Riseman, J. E. F.: Studies on the Action of Quinidine in Man: Arch. Int. Med. 71; 460 (April) 1943
3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1; 28-39 (Jan.) 1950
4. Bell, G. O.; Bradley, R. B.; and Hurxthal, L. M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case: Circulation, 1; 939 (April Part II) 1950

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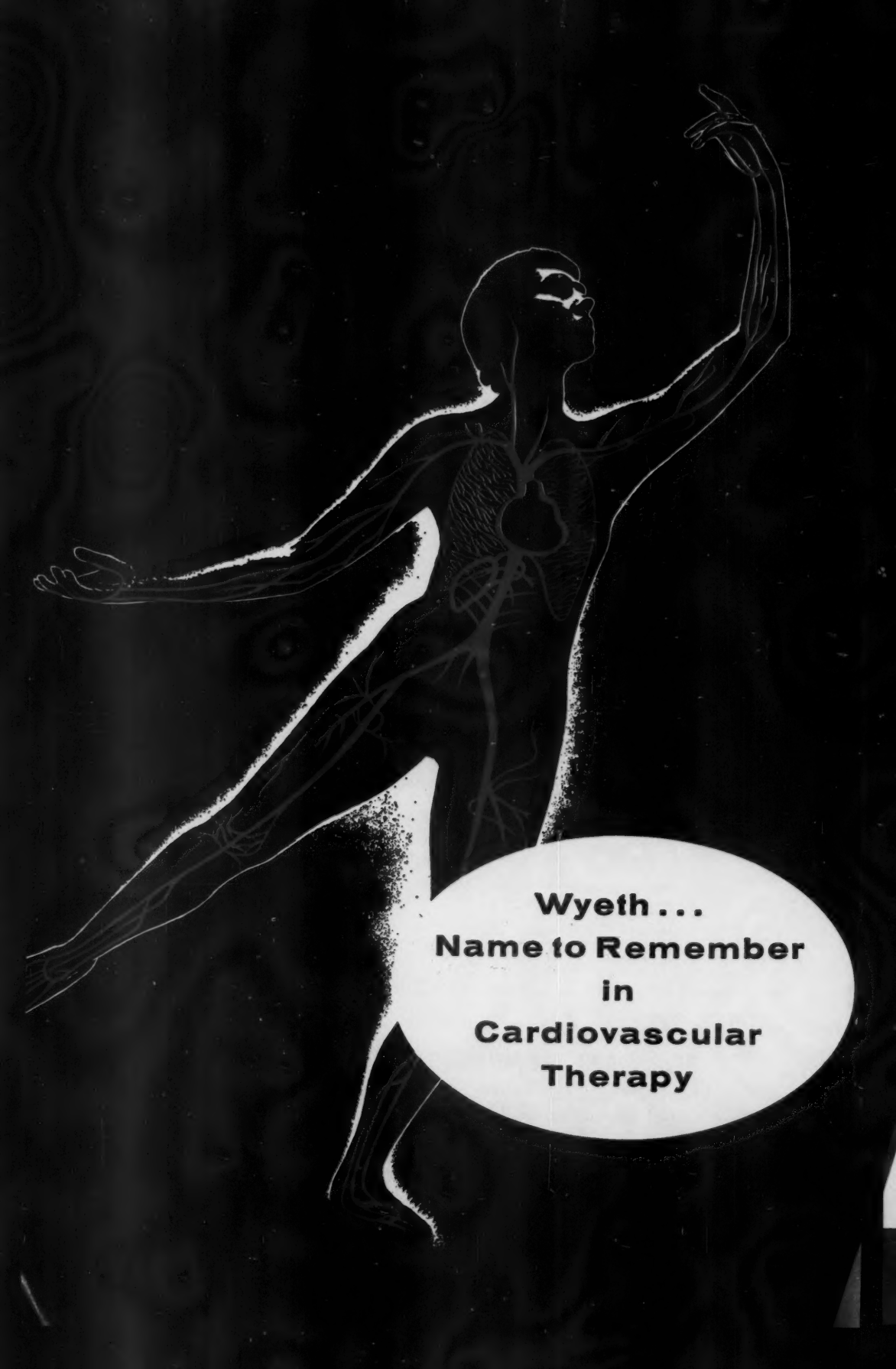


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. . . because among all Rauwolfia preparations Rauwiloid (alseroxylon) is maximally effective and maximally safe . . . because least dosage adjustment is necessary . . . because the incidence of depression is less . . . because up to 80% of patients with mild labile hypertension and many with more severe forms respond to Rauwiloid alone.

A Better Tranquilizer, too

. . . because Rauwiloid's *nonsoporific* sedative action relieves anxiety in a long list of unrelated diseases not necessarily associated with hypertension . . . without masking of symptoms . . . without impairing intellectual or psychomotor efficiency.

Dosage: Simply two 2 mg. tablets at bedtime. After full effect one tablet suffices.

Best first step when more potent drugs are needed

Rauwiloid is recognized as basal medication in all grades and types of hypertension. In combination with more potent agents it proves synergistic or potentiating, making smaller dosage effective and freer from side actions.

Rauwiloid®+Veriloid®
In moderate to severe hypertension this single-tablet combination permits long-term therapy with dependably stable response. Each tablet contains 1 mg. Rauwiloid and 3 mg. Veriloid. Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid®+ Hexamethonium
In severe, otherwise intractable hypertension this single-tablet combination provides smoother, less erratic response to hexamethonium. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, ½ tablet q.i.d.

Riker LOS ANGELES

In Boston Visit Our Exhibit, Booths 327 and 329

in rheumatic fever...

The Telltale Heart

Carditis is a most serious manifestation of rheumatic involvement. It tells a tale of initial or recurrent streptococcal attack—of organic damage and grave dysfunction. To protect the heart from these consequences is a major objective of BICILLIN prophylaxis.



Recommended by the American Heart Association:[1]

- **To prevent rheumatic-fever onset**—treatment of streptococcal infections:

Children—One intramuscular injection of 600,000 to 900,000 units

Adults—One intramuscular injection of 900,000 to 1,200,000 units

- **To prevent rheumatic-fever recurrence**—prophylaxis of streptococcal infections:

Rheumatic-fever patients—One intramuscular injection monthly of 1,200,000 units

1. American Heart Association: Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, Charles H. Rammelkamp, Chairman: Circulation *15*:154 (Jan.) 1957.

Wyeth®
Philadelphia 1, Pa.

INJECTION BICILLIN® LONG-ACTING

Benzathine Penicillin G (Dibenzylethylenediamine Dipenicillin G), Wyeth

MANTLE OF PROTECTION

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Your ℞ of **Sustagen Feedings q.2h.**

buffers acid
builds tissue
accelerates healing
provides a bland high protein diet

Sustagen®

PROVIDES FOOD FOR THE PATIENT
PROVIDES THERAPY FOR THE LESION



a peptic ulcer patient...

comfortable...well fed...**on the job!**

MEAD JOHNSON

SYMBOL OF SERVICE IN MEDICINE

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recognized

as a potent, specific anti-arthritic

established

by over 100 million patient days

substantiated

in more than 700 published reports

BUTAZOLIDIN®

(phenylbutazone GEIGY)

potent, specific anti-arthritic

Based on an impressive background of achievement attained over a period of four years involving both long-term and short-term therapy in all the major forms of arthritis, BUTAZOLIDIN is recognized as one of the most effective anti-arthritic agents currently available.

relieves pain

improves function

resolves inflammation

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with its use are urged to send for literature before prescribing it.

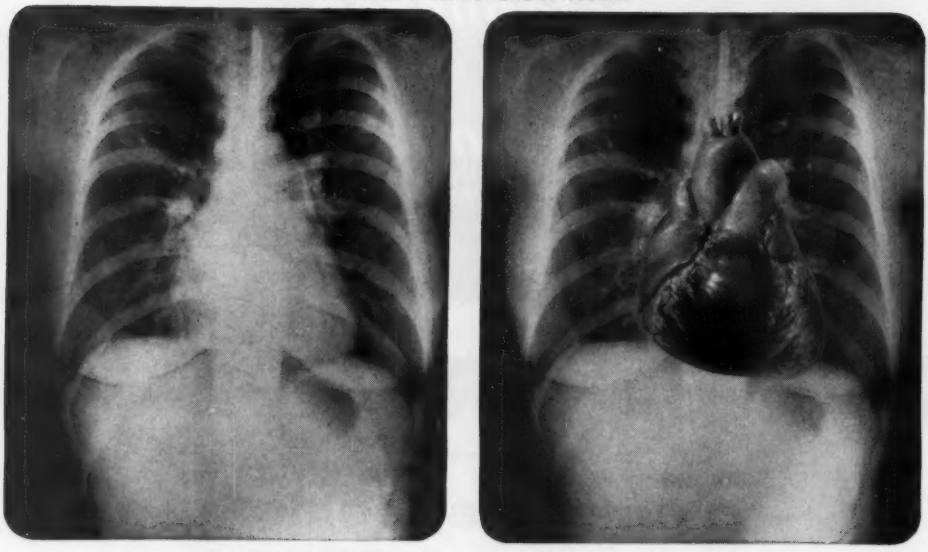
GEIGY

GEIGY PHARMACEUTICALS, Division of Geigy Chemical Corporation, New York 13, N. Y.

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"A GOOD PRESENT DAY ALL-PURPOSE DIGITALIS...GITALIGIN ...A PREPARATION WHICH HAS A WIDER MARGIN OF SAFETY..."*

VISUAL HEART CLINIC—ONE OF A SERIES



RHEUMATIC HEART DISEASE • MITRAL STENOSIS AND INSUFFICIENCY

ROENTGEN CONFIGURATION—Postero-anterior examination—moderate heart enlargement—right ventricular enlargement—prominence of pulmonary artery segment.

Taken from White Laboratories' Technical Exhibit, American Medical Association 105th Annual Meeting, Chicago, June 11-15, 1956.

Every year since 1950 when Batterman, et al., published the results of their study of 230 cardiac patients, clinical evidence has repeatedly confirmed the therapeutic advantages of GITALIGIN.

For initial digitalization and maintenance, GITALIGIN has proved to be "the digitalis of choice" for these significant reasons:

(1) Widest safety margin of any currently available digitalis glycoside (average therapeutic dose only 1/3 the toxic dose; in contrast, therapeutic doses of other preparations are approximately 2/3 toxic dose)
(2) Uniform clinical potency
(3) Moderate rate of dissipation
(4) Short latent period

Patients now being maintained with other cardiotonics can be easily switched to GITALIGIN: 0.5 mg. of GITALIGIN is approximately equivalent to 0.1 Gm. digitalis leaf, 0.1 mg. digitoxin, 0.5 mg. digoxin.

White's | GITALIGIN®

(WHITE'S BRAND OF AMORPHOUS GITALIN)

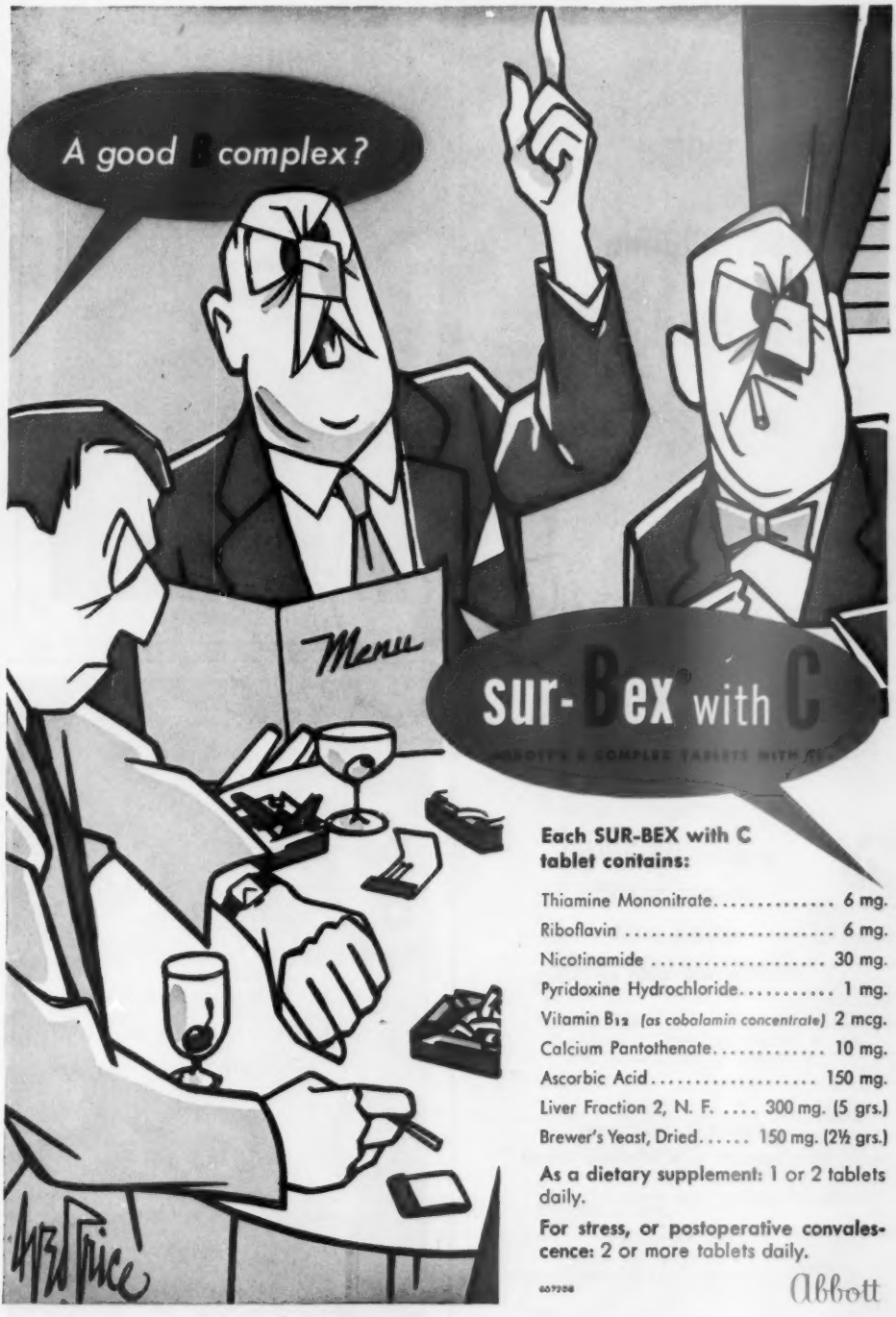
TABLETS—BOTTLES OF 30, 100, AND 1000 DROPS—30 CC. BOTTLES WITH DROPPER CALIBRATED FOR 0.05, 0.1, 0.2, 0.3, 0.4 AND 0.5 MG.

INJECTION—5 CC. AMPULS CONTAINING 2.5 MG. (0.5 MG. PER CC.) OF GITALIGIN. PACKAGES OF 3 AND 12 AMPULS.

*EHRLICH, J.C.: ARIZONA MED. 12:239 (JUNE) 1955. BIBLIOGRAPHY FURNISHED ON REQUEST

White Laboratories, Inc. Kenilworth, New Jersey

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Each SUR-BEX with C tablet contains:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} *(as cobalamin concentrate)*	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Liver Fraction 2, N. F.	300 mg. (5 grs.)
Brewer's Yeast, Dried	150 mg. (2½ grs.)

As a dietary supplement: 1 or 2 tablets daily.

For stress, or postoperative convalescence: 2 or more tablets daily.

607208

Abbott

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single
sulfonamide
specifically for
urinary tract
infections

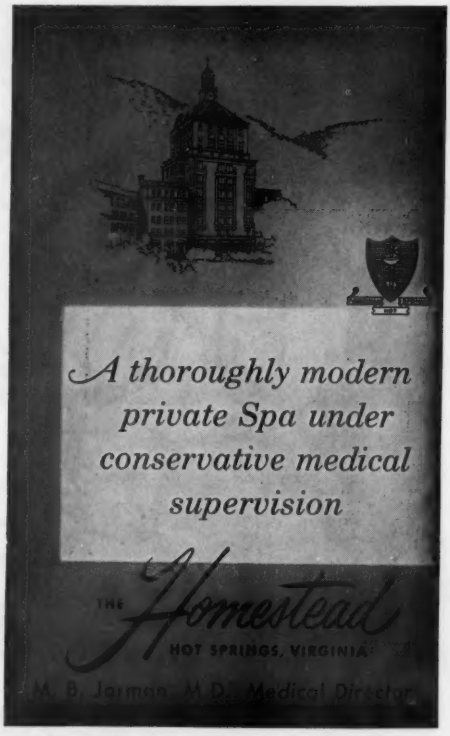
direct / effective
"THIOSULFIL"®
Brand of sulfamethizole

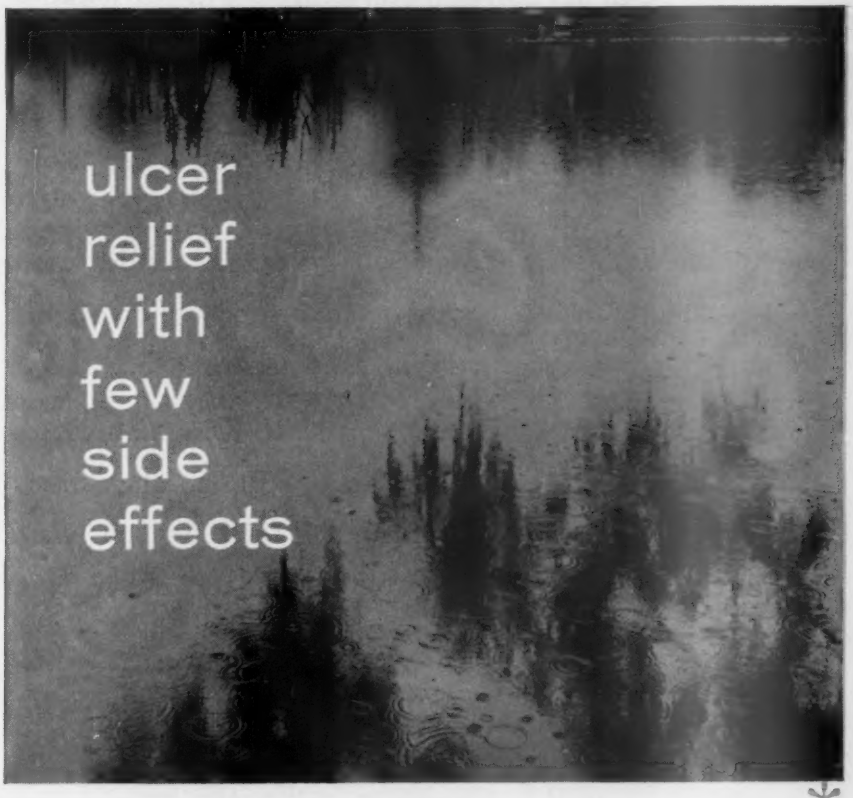
greater solubility
means rapid
action with
minimum side effects

AYERST LABORATORIES
New York, N. Y. • Montreal, Canada
5652

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PATHILON*

TRIDIHEXETHYL IODIDE LEDERLE

PATHILON is well tolerated in orally given doses and provides not only prompt clinical symptomatic relief but also effective inhibition of painful spasm at the ulcer site. Important to many patients, PATHILON is relatively inexpensive.

PATHILON is particularly useful in ulcer treatment because its peripheral atropine-like actions are associated with few side effects.[1] Side effects, if any, are usually not severe enough to warrant discontinuance of the drug.[2]

Recommended in the treatment of peptic ulcer, gastric hyperacidity and hypermotility, gastrointestinal spastic conditions such as spastic and irritable colon, functional diarrhea, pylorospasm, and hypermotility of the small intestine not associated with organic change.[3]

Available in three forms; *tablets* of 25 mg., plain (Pink) or with phenobarbital, 15 mg. (Blue), and *parenteral*, 10 mg./cc.—1 cc. ampuls.

1. *Evaluation of Drugs in the Treatment of Peptic Ulcer* by J. M. Ruffin, M.D.; D. Cayer, M.D.; J. S. Atwater, M.D., and B. G. Oren, M.D.: Exhibit at A.M.A. Meeting, Atlantic City, June, 1955.
2. Council on Pharmacy and Chemistry: *J.A.M.A.* 160:389 (Feb. 4) 1956.
3. Council on Pharmacy and Chemistry: *ibid.*

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

*REG. U. S. PAT. OFF.

In Boston Visit Our Exhibit, Booth 235



". . . best results were obtained with women 35 to 55 years of age, who complained of anxiety, insomnia, chronic fatigue and despondency."[1]

Many physicians have reported favorable results with 'Compazine' in the mild or moderate mental and emotional conditions often associated with the menopause.

For example, in a series of 84 patients, Knoch and Kirk report outstanding results in women 35 to 55. The authors state that after 'Compazine' treatment, these women "were no longer fatigued, were sleeping well, had increased energy and showed a lively interest in their surroundings."

'Compazine' is S.K.F.'s new tranquilizer and antiemetic for everyday practice.

'Compazine' has shown minimal side effects.

*Compazine**

a true tranquilizing agent

Smith, Kline & French Laboratories, Philadelphia

1. Knoch, H.R., and Kirk, R.: Proclorperazine—A New Agent for the Treatment of Psychic Stress, in manuscript.

*Trademark for proclorperazine, S.K.F.

in biliary tract disorders

CHOLOGRAFIN

intravenously provides more diagnostic information than oral contrast media

More consistently than oral contrast media, intravenous Cholografin visualizes the entire extrahepatic biliary system. It does this "whether or not the gallbladder functions or is even present."[1]

After cholecystectomy, moderate to severe symptoms may persist in 10 to 25 per cent of patients whose gallbladders are removed because of cholelithiasis, and in 50 per cent of those whose gallbladders are removed for so-called noncalculous gallbladder disease.[2] In these patients, Cholografin may reveal strictures, calculi in the common or hepatic ducts, or cystic duct remnants. It may also reveal dilatation of the common duct (presumptive evidence of dyskinesia or organic obstruction).

Preoperative visualization of the gallbladder and extrahepatic ducts, even when the gallbladder is not functioning, means that Cholografin can frequently reveal radiolucent calculi in the gallbladder, hepatic and common ducts. It can also reveal anomalies and be of diagnostic value when neoplasm is suspected. Biliary surgery can now be based on more complete diagnostic information than can be provided by oral media.

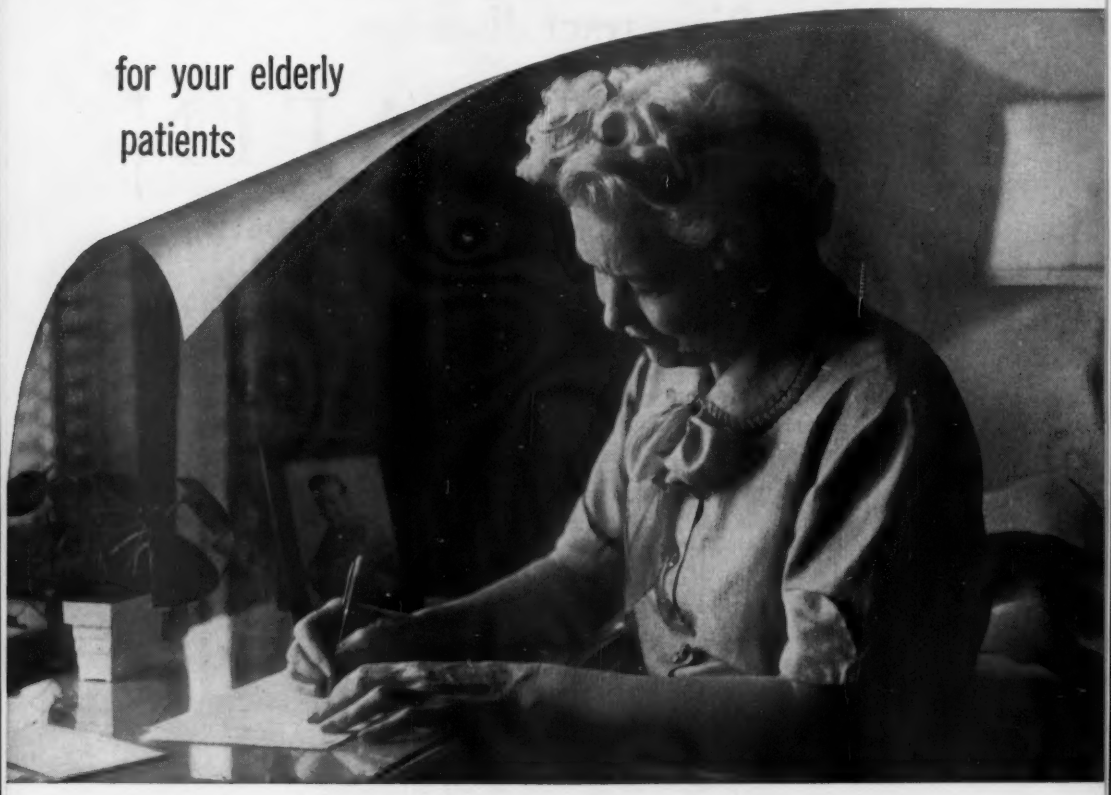
Cholografin, Squibb iodipamide, is available as *Cholografin Sodium*, in cartons of two 20-ml. ampuls with two 1-ml. ampuls for sensitivity testing, and *Cholografin Methylglucamine*, in cartons containing one 20-ml. ampul with one 1-ml. ampul for sensitivity testing.

SQUIBB

1. Glenn, F., Evans, J., Hill, M., and McClenahan, J.: Intravenous cholangiography. Ann. Surg. 140:600 (Oct.) 1954. 2. Sandweiss, D. J., and Fulton, H.: Intravenous cholangiography. J.A.M.A. 159:998 (Nov. 5) 1955.

"CHOLOGRAFIN"® IS A SQUIBB TRADEMARK

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safe and sure laxation

Agoral relieves constipation gently, without strain. A dose taken at bedtime almost always produces results the next morning. A patient taking Agoral can follow his or her normal daily routine because Agoral does not provoke the sudden urge induced by strong laxatives.

Excellent in geriatrics, Agoral solves one of the major, recurrent problems in this field, acting gently and positively. Agoral is also well suited to all other cases of acute and chronic constipation, where straining or purges are to be avoided: Postoperatively, during and after pregnancy, and in bedridden patients.

Agoral mixes readily and uniformly with the intestinal contents during its passage through the tract. It aids in the retention of fluid in the fecal column, affords lubrication and provides mild peristaltic stimulation. Agoral causes no sudden, uncomfortable griping, distention or stomach distress. Used for prompt relief, it is nonhabit-forming and may be prescribed for protracted periods.

Dosage: At bedtime, ½ to 1 tablespoonful. Contraindications: Symptoms of appendicitis; idiosyncrasy to phenolphthalein.

Supplied: Bottles of 6, 10 and 16 fluidounces; and as Agoral Plain (without phenolphthalein), bottles of 6 and 16 fluidounces.

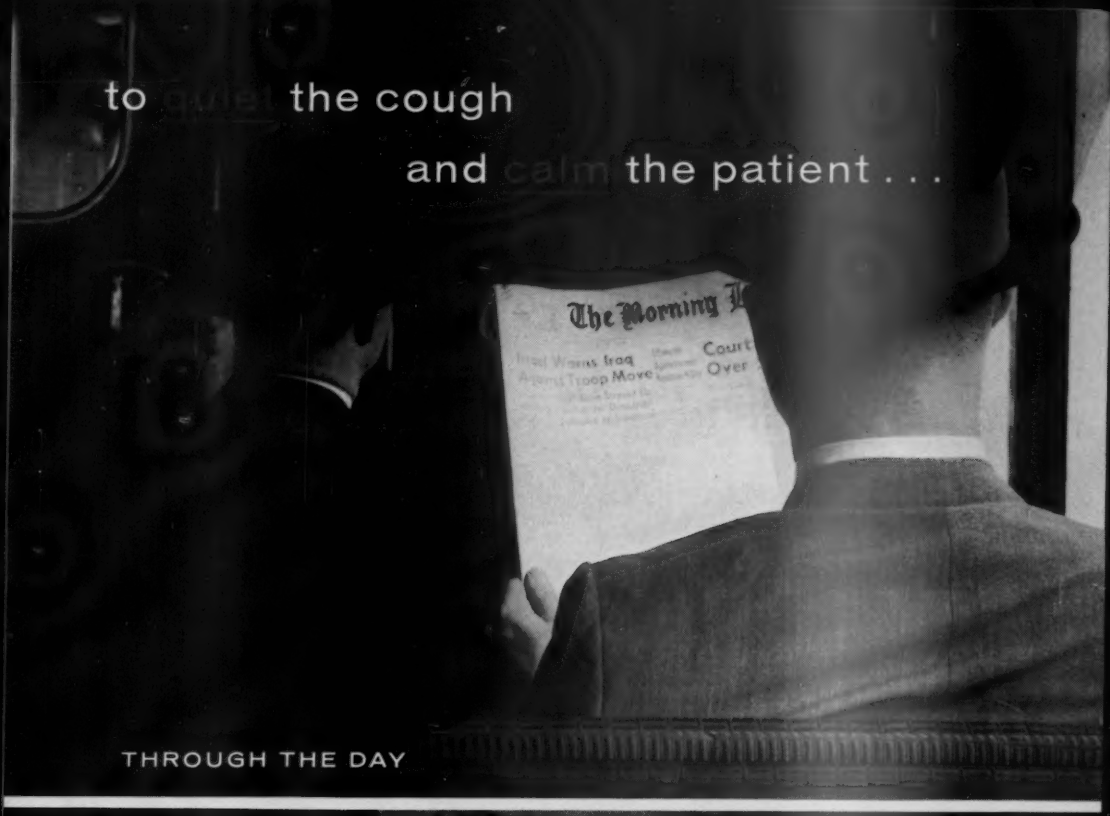
Agoral® *the laxative to meet all needs*

mineral oil emulsion with phenolphthalein

WARNER-CHILCOTT
100 YEARS OF SERVICE TO THE MEDICAL PROFESSION

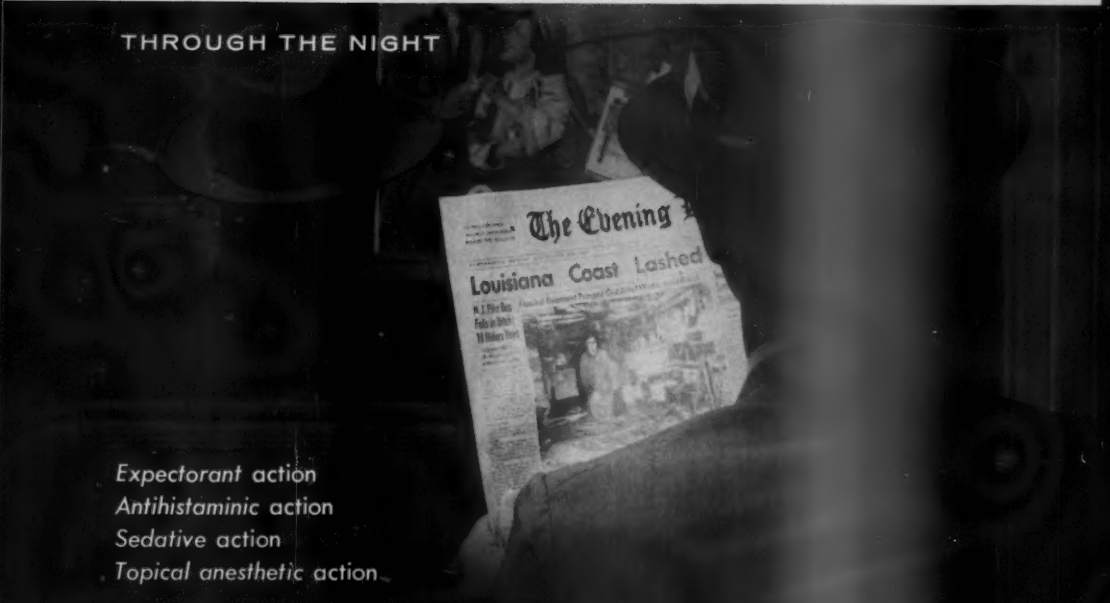
to quiet the cough

and calm the patient . . .



THROUGH THE DAY

THROUGH THE NIGHT



Expectorant action
Antihistaminic action
Sedative action
Topical anesthetic action

PHENERGAN

EXPECTORANT

Promethazine Expectorant with Codeine Plain (without Codeine)

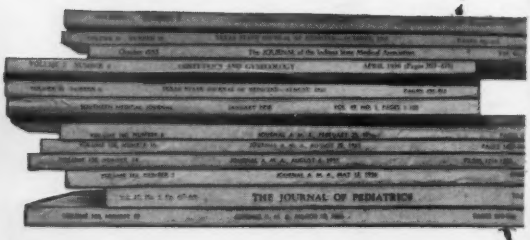
Wyeth®
Philadelphia 1, Pa.

"The average female

is borderline

iron deficient..."[3]

IN MENSTRUAL



The bibliography specifies

1. Moore, C.V., and Dubach, R.: J.A.M.A. 162:197 (Sept. 15) 1956.
2. Holly, R.G.: Obstet. and Gynec. 2:124 (Aug.) 1953.
3. Ausman, D.C.: Journal-Lancet 76:290 (Oct.) 1956.

LLOYD *Brothers, Inc.*

Cincinnati 3, Ohio

ANEMIA...

Evidence shows that practically every menstruating female is in a state of precarious iron balance. Thus the iron deficiency state, due to even *normal* menstrual losses, is an extremely common occurrence.[1, 2]

Correction of this iron deficiency state results in real benefits to the tired, rundown female patient.

Strikingly superior clinical responses in menstrual anemia have been reported with RONCOVITE.[3] These results can be explained by the increased absorption and utilization of iron due to the improved bone marrow activity provided only by RONCOVITE.

Roncovite Tablets (*in menstrual anemia*):

Maximum Adult Dosage: One tablet after each meal and at bedtime.

Bottles of 100 tablets.

Literature available to physicians on request.

Roncovite®

THE ORIGINAL, CLINICALLY PROVED COBALT-IRON PRODUCT

Sparine*

HYDROCHLORIDE

10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride

*Trademark

Promazine Hydrochloride, Wyeth

THE ALCOHOLIC

SPARINE is an agent of prompt, predictable, and potent action in controlling withdrawal symptoms. Often, in selected cases under the adequate supervision of the family physician, it may afford *home control* of postalcoholic agitation and hyperactivity.[1]

SPARINE is a well-tolerated and dependable agent when used according to directions. It may be administered intravenously, intramuscularly, or orally.

Parenteral use offers

(1) minimal injection pain;
(2) no tissue necrosis at the injection site;
(3) potency of 50 mg. per cc.;
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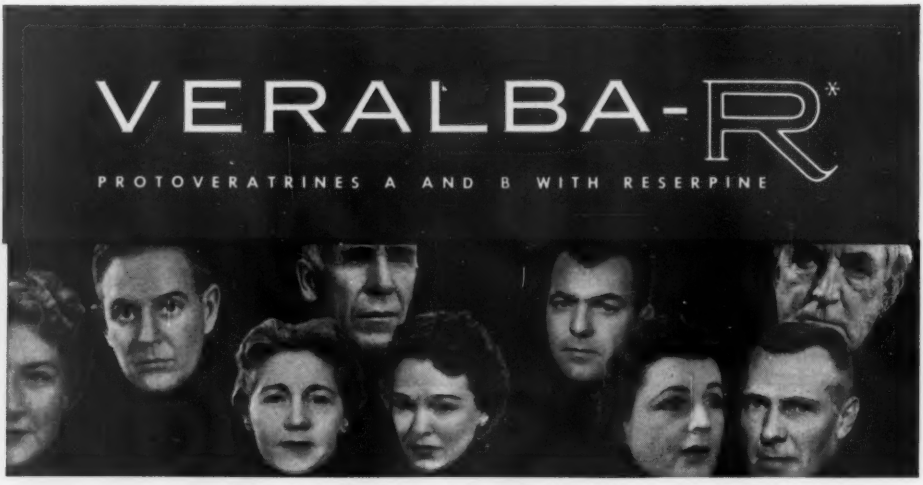
Professional literature available upon request.

1. Figurelli, F.A.: Indust. Med. & Surg. 25:376 (Aug.) 1956.

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Conservative therapy in hypertension can be made more effective



IN MANY OF YOUR HYPERTENSIVE PATIENTS, conservative treatment with reserpine can be made more effective by placing the patient on safe combination therapy.

EFFECTIVE. When combined with reserpine, the blood pressure lowering effects of protoveratrines A and B can be achieved with smaller dosage, and with marked decrease in annoying side actions.

SAFE. Veralba/R is many physicians' choice of combination therapy. It can be used routinely without causing postural hypotension or impairing the blood supply to the heart, brain and other vital organs. Dosage is simple.



ACCURATE. Veralba/R potency is precisely defined by chemical assay. All active ingredients are in purified, crystalline form.

Each Veralba/R tablet contains 0.4 mg. of protoveratrines and 0.08 mg. of reserpine. Bottles of 100 and 1000 scored tablets.

*Trademark

PITMAN-MOORE COMPANY, *Division of Allied Laboratories, Inc.,* **Indianapolis 6, Indiana**

THE GRAY PHARMACEUTICAL CO., INC.
pioneer in glutamate research and geriatric therapy,
is pleased to announce new therapies for hepatic coma

Glutavene T.M. & Glutavene-K T.M.
(intravenous solution of sodium L-glutamate, Gray) (intravenous solution of sodium-potassium L-glutamate, Gray)

NEW THERAPIES FOR HEPATIC COMA

The effectiveness of GLUTAVENE and GLUTAVENE-K in relieving acute and chronic encephalopathy due to ammonia intoxication has been confirmed by recent clinical reports.[2-9] In a significant number of cases, an appreciable drop in the blood level of ammonia occurs and is attended by improvement in the level of consciousness. "...over half the patients in these combined groups were restored to a completely normal neurologic status."[1]

Daily Dosage: 1 vial of GLUTAVENE or GLUTAVENE-K diluted in 1000 ml. of 5 or 10% dextrose in water for injection, infused intravenously over a 4 hour period.

Supply: GLUTAVENE (sodium L-glutamate) and GLUTAVENE-K (sodium-potassium L-glutamate), each equivalent to 25 grams L-glutamic acid, in 100 ml. vials.

In Cases of Emergency: Special arrangements have been made by the Gray Pharmaceutical Co., Inc., for immediate delivery of GLUTAVENE and GLUTAVENE-K. Address: Gray Pharmaceutical Co., Inc., 50 Hunt Street, Newton 58, Massachusetts. Request for additional information will be promptly honored by our Medical Department.

References: 1. McDermott, W. V., Jr., et al.: New England J. Med. 253:1093 (Dec. 22) 1955. 2. Council on Pharmacy and Chemistry: J.A.M.A. 161:458 (June 2) 1956. 3. Eiseman, B., et al.: Am. J. Med. 20:890 (June) 1956. 4. Walshe, J. M.: Lancet, p. 1075 (May 30) 1953. 5. Woodrow, C. E., Froome, L.: Lancet, p. 1290 (Dec. 19) 1953. 6. Walley, R. V.: Lancet p. 157 (Jan. 16) 1954. 7. Riddell, A. G., McDermott, W. V., Jr.: Lancet, p. 1263 (June 19) 1954. 8. DeGroote, J., et al.: Lancet, p. 722 (Oct. 1) 1955. 9. Chaikin, N. W., et al.: Am. J. Gastroenterol. 26:258 (Sept.) 1956.

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PRODUCTS OF RESEARCH FOR MEDICINE

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"MYSOLINE" effectively controls grand mal and psychomotor seizures

Control of seizures was obtained in 57 per cent of 97 grand mal patients where "MYSOLINE" was used as initial therapy; an additional 22 per cent were improved.[1] In patients refractory to previous standard medication, Pence[2] obtained improvement to complete control in 70 per cent of cases. In his study, "MYSOLINE" was added to current medication and in some cases this was replaced by "MYSOLINE" alone. He observed that patients can usually remain under control without necessitating dosage increases above the established maintenance level. "Grand mal convulsions, psychomotor automatisms and focal motor convulsive disorders respond most readily to this drug."[3]

NOTABLY FREE FROM SERIOUS TOXIC EFFECTS

Urinalyses and blood counts during therapy failed to reveal any abnormalities.[2] When side reactions do occur, they are usually mild and transient and tend to disappear as therapy is continued.

"MYSOLINE"®

Brand of Primidone

in epilepsy

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

LITERATURE ON REQUEST

1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
2. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.
3. Berman, B. A.: Am. J. Psychiat. *112*:541 (Jan.) 1956.

Ayerst Laboratories • New York, N.Y. • Montreal, Canada

"Mysoline" is available in the United States by arrangement with Imperial Chemical (Pharmaceuticals) Limited.

5656

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Medihaler

Means self-powered, uniform, measured-dose inhalation therapy . . . made possible by specially designed metered-dose valve . . .



Medihaler

Means notably safe and effective therapy when indicated for children. Medication is in leakproof plastic coated bottles . . .





Medihaler

Means true nebulization. Each measured dose provides 80 per cent of its particles in the optimal size range—0.5 to 4 microns radius—insuring effective penetration of the respiratory tract.

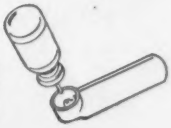


Medihaler

Medication and Adapter fit into neat plastic case, convenient for pocket or purse . . .

Medihaler

Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate . . .



Medihaler

Means greater economy—no costly glass nebulizers to replace, and one or two inhalations usually suffices for prompt relief.



Medihaler

The Unique Measured-Dose Inhalation Method

In Asthma

For Rapid Relief of Acute or Continuing Bronchospasm

Medihaler-Epi™

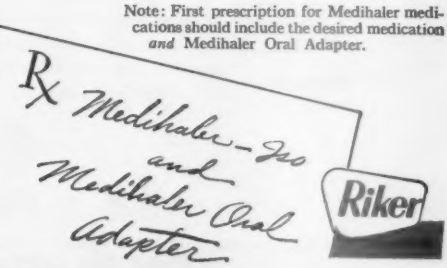
Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

Medihaler-Iso™

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Note: First prescription for Medihaler medications should include the desired medication *and* Medihaler Oral Adapter.



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For Infectious Diarrhea

THE FULL ATTACK...

Antibacterial

Adsorptive

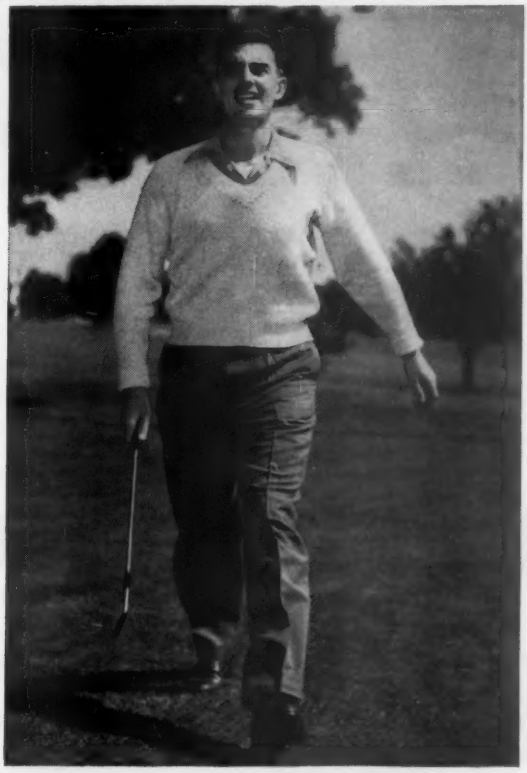
Protective

Streptomagma combats bacterial diarrhea with multiple forces. It offers dihydrostreptomycin to control the streptomycin-susceptible organisms. Simultaneously, its pectin, kaolin, and alumina gel soothe the irritated bowel, promote development of well-formed stools, and aid in the removal of bacterial toxins and irritants.

Wyeth®
Philadelphia 1, Pa.

STREPTOMAGMA®
Dihydrostreptomycin Sulfate and Pectin with Kaolin in Alumina Gel

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Back to par after biliary colic

DEPROPANEX

DEPROTEINATED PANCREATIC EXTRACT

When you give DEPROPANEX in biliary colic you obtain basic—not narcotic—relief of spasm in three minutes. Action is on the smooth muscle itself. Ureteral and renal colic respond equally promptly. Cystoscopy and other instrumental procedures are easier because of muscular relaxation. Postoperatively DEPROPANEX helps control paralytic ileus.

MSD

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DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

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quick

YES

or

NO

test

CLINISTIX®

BRAND Reagent Strips

specific enzyme test for urine glucose



◀ routine office testing
bottles of 60 CLINISTIX Reagent Strips



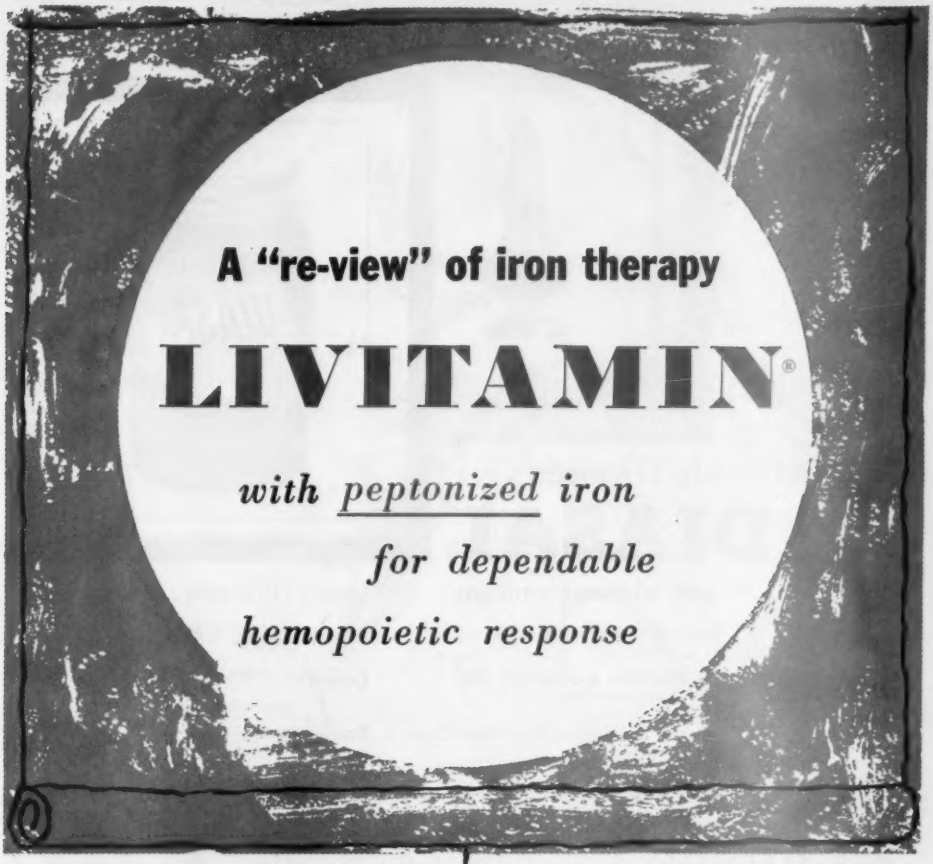
daily check by mild diabetics, well-controlled diabetics ▶
packets of 30 CLINISTIX Reagent Strips
in new protective foil pouch

utmost simplicity and convenience...A firm, easily handled CLINISTIX Reagent Strip is moistened with urine.

qualitative accuracy...CLINISTIX Reagent Strip turns blue only if glucose is present. No blue color—no glucose!

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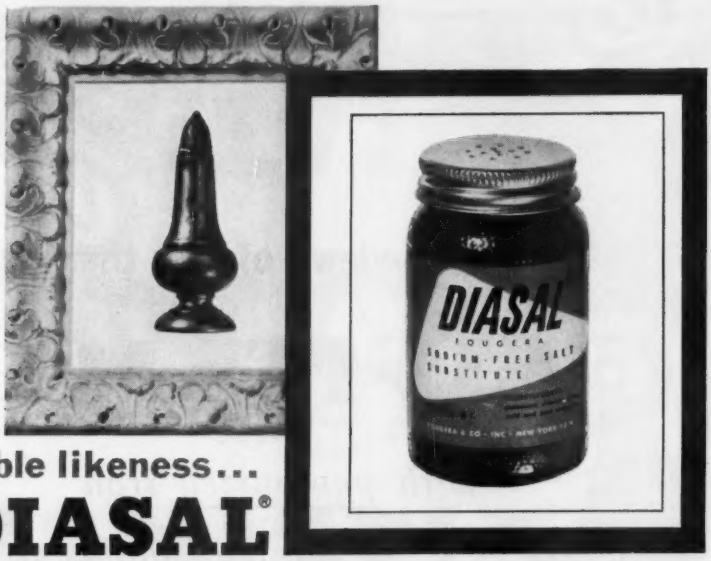
*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate. Read before the American Association for the Advancement of Science, Atlanta, Georgia, December, 1955

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*Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. 160:1221, 1956.

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Lemere, F.: Northwest Med. **54**: *1098, 1955.*

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Sokoloff, O.J.: A.M.A. Arch. Dermat. In press.

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Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. **17**: *19, 1956.*

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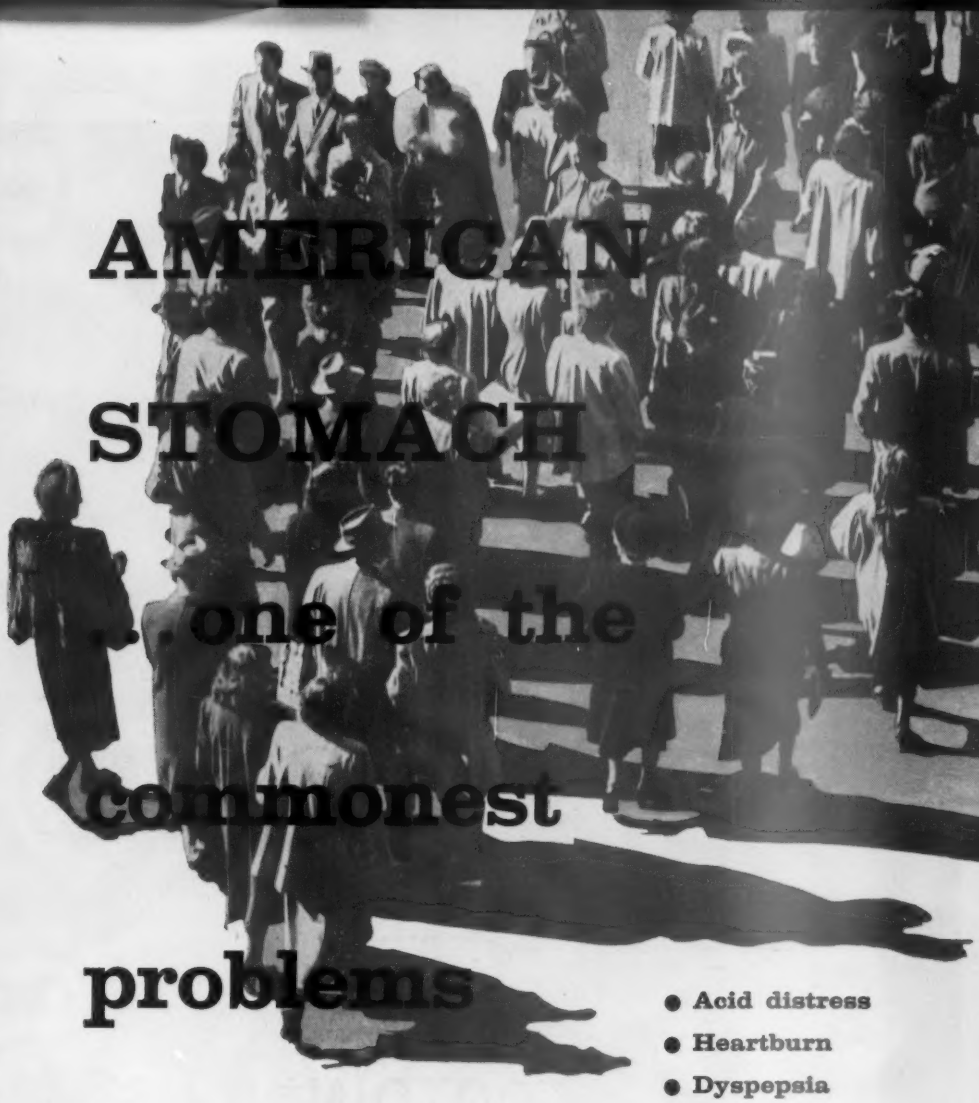
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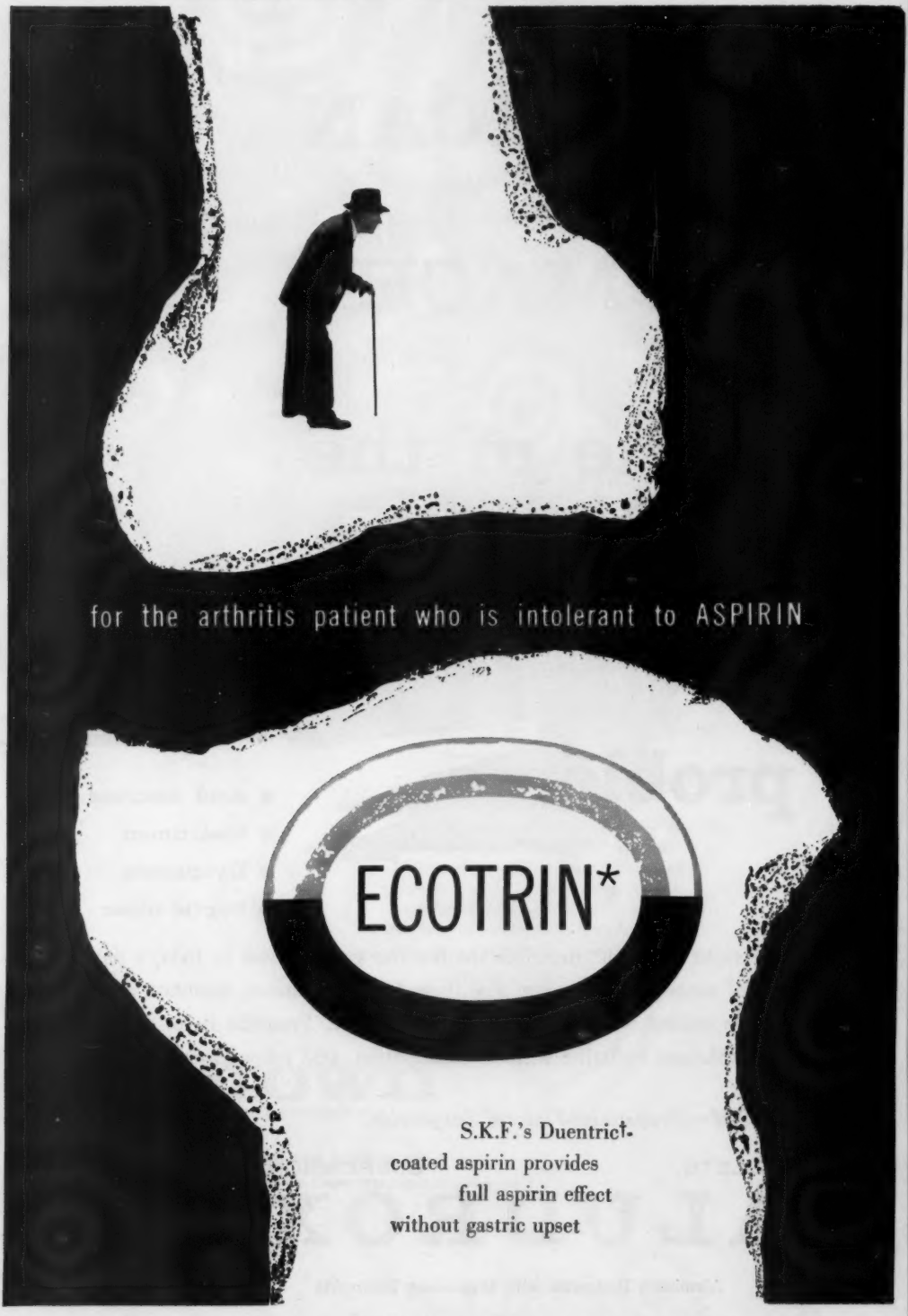
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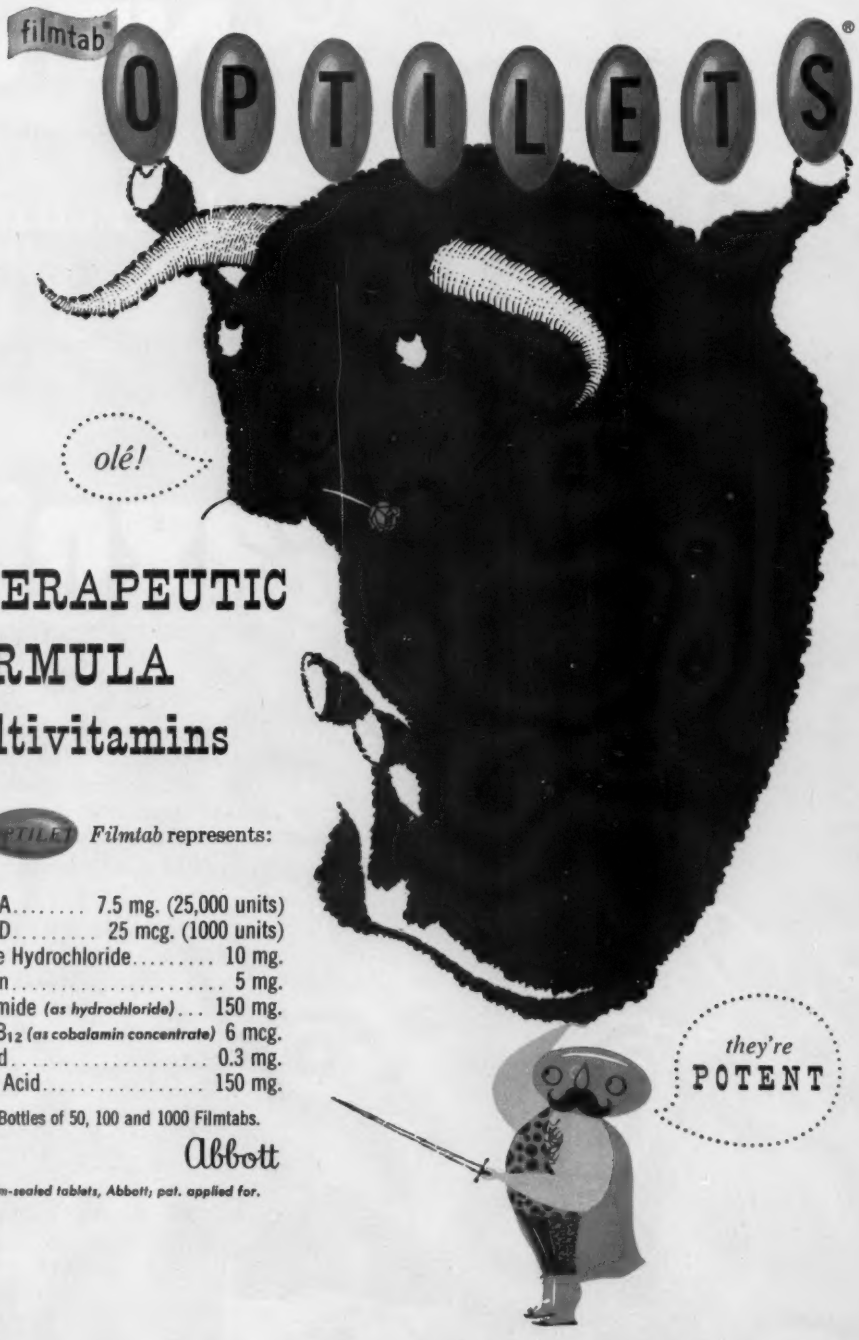
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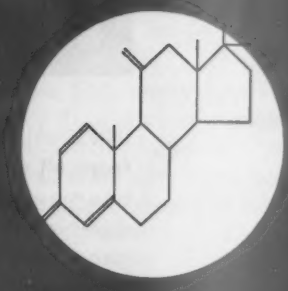
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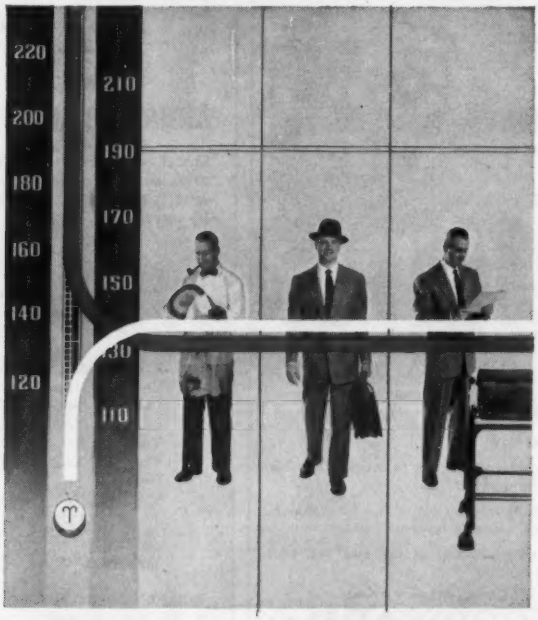
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1. Bollet, A.J., Black, R., and Bunim, J.J.: J.A.M.A. *158*:459 (June 11) 1955.

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ANNALS OF
INTERNAL MEDICINE

VOLUME 46 FEBRUARY, 1957 NUMBER 2

TUBERCULOSIS AMONG UNIVERSITY STUDENTS: A 35 YEAR EXPERIENCE *

By J. ARTHUR MYERS, F.A.C.P., RUTH E. BOYNTON and HAROLD S. DIEHL, *Minneapolis, Minnesota*

IN the fall of 1920 a clinic for diagnosis and treatment of diseases of the chest was established at the University of Minnesota Students' Health Service. This clinic has been in continuous operation for one or two hours each day through the regular school years and summers. During that period 155,021 students, exclusive of the Graduate School, have enrolled on the Minneapolis and St. Paul campuses. Admission to the chest clinic has been limited to students and personnel, both professional and nonprofessional, referred by other members of the medical staff, and those who personally made requests for examinations and treatment.

CLINIC PROCEDURES AND FINDINGS

Since this clinic was established, 7,530 students and faculty members have been examined for chest conditions. Many of them were reëxamined on numerous occasions, and treatment was administered as indicated. Although numerous minor and major nontuberculous conditions have been diagnosed and treated, tuberculosis has been the most prevalent and time-consuming. Therefore, this paper is confined to that disease.

TUBERCULOSIS

In 1920 there were so many cases of clinical tuberculosis on the campus that this disease was not only the main reason for establishing the clinic,

* Received for publication March 23, 1956.
From the Students' Health Service, School of Public Health, and Department of Internal Medicine, University of Minnesota.
Prepared with the aid of the H. Longstreet Taylor Foundation, established by the Minnesota Tuberculosis and Health Association.
Requests for reprints should be addressed to J. Arthur Myers, M.D., University of Minnesota School of Public Health, 1316 Mayo Memorial Building, Minneapolis 14, Minnesota.

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but also consumed most of the time of its staff. Diagnosis usually was based on symptoms, physical signs and demonstration of tubercle bacilli. X-ray film inspection of the chest was employed only when symptoms and/or abnormal physical signs were elicited.

In another clinic directed by one of us (J. A. M.), where x-ray film inspection was made of the chests of all admissions, shadow-casting lesions were often revealed in the lungs of persons free from symptoms and abnormal signs. Therefore, x-ray film inspection of the chest later became routine in our Students' Health Service clinic.

When the limitations of the x-ray film became apparent, and it was realized that only gross lesions with adequate consistency and suitably located cast demonstrable shadows, the tuberculin test was recognized as the most refined diagnostic agent, since it justified the diagnosis of first-infection type of tuberculosis in the absence of x-ray shadows. Inasmuch as tuberculin sensitivity always precedes development of gross clinical lesions, x-ray film inspection was recognized as an essential part of periodic examinations of tuberculin reactors to detect the location of such lesions as early as possible.

Recovery of tubercle bacilli has been considered our last court of appeal. When acid-fast bacilli were found in sputum or in gastric or bronchial washings, their pathogenicity had to be determined by culture or, preferably by animal inoculation.

The tuberculin reactor who presents an x-ray shadow-casting lesion in an apex of a lung from which tubercle bacilli are not recovered on repeated trials by all methods is the bane of the diagnostician. Although until recently roentgenologists almost universally reported such shadow-casting lesions as tuberculous, clinicians knew from postmortem experience that many of them were nontuberculous. Now that pulmonary biopsy is possible, we have occasionally found it necessary to resort to this procedure.

Determination of activity of tuberculous pulmonary lesions may be exceedingly difficult. One cannot always be guided by x-ray shadows. When a shadow-casting lesion is first seen, one should never attempt to determine activity from the shadow alone. Such a lesion may have been present without change for many years. Again, it may have recently evolved. After a lesion is found by the shadow it casts, subsequent x-ray film inspections made periodically are of help only if there is evidence that the lesion has become larger or smaller, or that changes within it have occurred.

A lesion may appear from its shadow to be exactly the same year after year, and therefore is considered well stabilized, even though there is definite activity within which is not detectable by shadows. For example, a student had such a lesion in evidence on entrance to school which showed no change in shadow throughout her course. However, nine years after this lesion was first detected, and without apparent x-ray change, she suddenly had a pulmonary hemorrhage, after which evidence of excavation was seen in the

center of the lesion. Necrotic tissue had discharged into a bronchial ramification, with no change being in evidence at the periphery of the lesion.

Another student whose lesion had remained stable from the x-ray shadow standpoint was advised on leaving school to have frequent periodic examinations. This lesion later showed evidence of progression, and is cited to emphasize that no tuberculous lesion is to be trusted, no matter how inactive it appears to be at a given moment or how long it has appeared so.

The erythrocyte sedimentation rate has been used extensively in our clinic, but since it is not specific one is rarely certain that acceleration is due to a pulmonary lesion under consideration. However, if one attempts to rule out all other possibilities and the rate is still markedly accelerated and persists, it may be accepted as reasonably good evidence that the given lesion is active.

The finding of acid-fast bacilli, even if they prove to be tubercle bacilli, in an occasional gastric washing specimen, with no other significant evidence of progressive tuberculosis, has not received particular emphasis in our clinic. In epidemiologic work we have not yet seen a tuberculin converter for whom there was proof that a person with tubercle bacilli found only in gastric washings was responsible.

Among the 7,530 individuals examined since the fall of 1920, the diagnosis of reinfection or clinical type of pulmonary tuberculosis was made in 1,055. It is probable that some such diagnoses, particularly in the earlier years of this work, were in error, inasmuch as "x-ray diagnoses" were sometimes accepted when tubercle bacilli were not recovered. In more recent years we have insisted upon more thorough documentation of cases. Even with this, we have been guilty occasionally of making presumptive diagnoses of tuberculosis without recovery of tubercle bacilli and without biopsy.

Our patients with diagnoses of tuberculosis fall into two groups. Group one consists of those who had clinical disease before entering school. In some of them the lesions had been stabilized, while others were still on treatment, including artificial pneumothorax. When this clinic was established, and for some years thereafter, we received a sizable number of students who were World War I veterans and who had been or were being treated by the United States Public Health Service and, later, by the United States Veterans Bureau. Since World War II a sizable number who have been treated by and are still under the observation of the United States Veterans Administration have been enrolled in this University. Many of them have been sent here on a rehabilitation or reëducation basis, and they are still under close medical observation by the Veterans Administration.

Inasmuch as tuberculosis is notoriously a relapsing disease, we have felt the responsibility of keeping close check on those who entered school after having had clinical tuberculosis, although they apparently had recovered. Practically all tuberculous students under the jurisdiction of the Veterans Administration, local civilian sanatoriums and private physicians have been

examined in our clinic on admission to school. Thereafter, those in charge have supplied us with reports of periodic examinations at three- to six-month intervals. Before such periodic examinations were required some catastrophies occurred on the campus. These consisted of reactivation of old lesions or development of new ones which became contagious without our knowledge. Now, such situations are usually detected and managed promptly.

The second group of students with clinical tuberculosis consisted of those who had disease first found on entrance, or those in whom it evolved while they were on the campus.

Management and Treatment of Pulmonary Tuberculosis

One of the chief objects of this clinic has been to prevent dissemination of tubercle bacilli by students and personnel. Among students who had previously unknown demonstrable lesions on entrance to school, it has been impossible to determine the duration of the disease except in a few who had previously had periodic tuberculin testing. However, this number has markedly increased during the past decade. If tubercle bacilli were promptly recovered, treatment was immediately recommended. If not, and if the lesions were minimal in extent, careful observation was recommended, with x-ray films and bacteriologic studies of gastric washings. If the lesions were found to be well stabilized, students were permitted to remain in school, with frequent periodic examinations.

Those found to have previously unknown contagious advanced pulmonary tuberculosis on entrance, as well as those in whom it evolved while in school, were advised to be hospitalized promptly. When necessary, they were admitted to our Students' Health Service hospital until transfer to sanatoriums could be arranged.

There were students who had been treated before their first admission to the University and who were still receiving artificial pneumothorax. Others, whose disease became clinical while in school and who were sent to sanatoriums, were returned to us while still on this treatment. This was continued as long as it seemed indicated.

Since 1920 we have frequently instituted artificial pneumothorax for minimal to moderately advanced pulmonary lesions. Adequate collapse of the involved area usually promptly rendered the sputum or gastric washings free from tubercle bacilli and prevented many from developing positive sputum. A sizable number of students were so treated on the campus with little interruption of school work and were graduated with their classes.

In relatively few, serious complications occurred such as tuberculous pneumonia in the contralateral lung, and mixed infection empyema in the pneumothorax cavity. In recent years antituberculosis drugs have been administered for a week or so before pneumothorax was instituted and have been continued simultaneously with the collapse. Although the number of such cases has decreased over the past decade, we have seen no serious complication develop.

Since 1948 the majority of our students treated for tuberculosis before entering school have had pulmonary resections. Most of them have been treated in Veterans Administration hospitals. A minority group has received similar treatment in civilian sanatoriums and hospitals.

In a few whose disease evolved while in school, we have administered antituberculosis drugs and recommended surgical resection in the University or other hospitals. These persons had lesions for which artificial pneumothorax was not indicated. Resection of a tuberculous lesion, whether it be small or extensive, does not cure tuberculosis. It only removes the lesion that is offending at the time, but one or more remaining lesions not yet demonstrable as to location may later attain such proportions. Therefore, periodic examinations are continued.

Primary Tuberculosis

Diagnosis and Course: In addition to students who presented the clinical reinfection type of pulmonary tuberculosis, we have had sizable numbers who developed primary disease while in school. A preponderance of them were in the Schools of Nursing and Medicine. A relatively small percentage of this group presented primary infiltrates so located and of such size and consistency as to cast visible shadows on x-ray films. Such x-ray shadows could not be differentiated from those of a reinfection type of lesion. It was only when the individual had a tuberculin testing record and had recently converted that one could be certain the new lesion was of the first-infection type. If there had been no periodic tuberculin testing, the course of the lesion often enabled us to determine its type. After they are first seen, primary infiltrates rarely increase in size. Shadows may appear to be the same month after month, then slowly resolve until they are no longer in evidence on x-ray film or, at most, leave small densities suggesting fibrous deposits. In some of these areas, which even become invisible on x-ray films, there later appear calcific deposits, and at about the same time such deposits may be seen in regional lymph nodes.

In the occasional primary infiltrate a small excavation may be seen. In such cases pulmonary hemorrhage has been observed, and it is not unusual to recover tubercle bacilli from gastric or bronchial washings for a brief time. We have not seen a case of so-called immediately progressive primary infiltrate among our students.

Thus primary tuberculosis acquired by young adults behaved in the same manner as we had so often observed in children.

Treatment: During our earlier observations it was thought that demonstrable lesions in the lungs of students were usually of the reinfection type, because it was assumed that practically all adults had been infected as children. Later, much was heard about immediately progressive primary lesions among young adults. We therefore recommended treatment of all lesions that appeared to be of recent evolution. Some were placed on long

periods of hospitalization, others received artificial pneumothorax; still others, because of absence of symptoms, refused treatment. The end result of the primary lesions per se was the same in each group. The body's defense mechanism, with or without attempted aid by physicians, brought the lesions under control in the same manner. After this observation, we discontinued treatment for primary pulmonary infiltrates.

In recent years, some primary pulmonary infiltrates have been resected. In view of our observations, we have seen no indication for such treatment for either immediate or remote results. With the initial invasion with tubercle bacilli, the organisms are focalized in many places in the body. To remove one focus which happens to be demonstrable by the x-ray shadow it casts does not cure the disease in any sense, nor is there evidence that it prevents later endogenous reinfections from remaining lesions of primary complexes.

Although primary lesions were regularly observed to come under control without causing significant illness, we knew that tubercle bacilli often remained alive and were harbored in their necrotic components. Therefore, the disease was not cured. It was also known that apparently well walled-off primary lesions in lungs, regional lymph nodes and other organs often at some later time liberated tubercle bacilli on allergic tissues, thus resulting in endogenous reinfections which frequently became clinically significant and contagious.

Our lament was that no method of treatment was available to prevent endogenous reinfections. Once tubercle bacilli invaded human tissues and set up primary foci in various organs, we were helpless to do more than wait and watch for appearance of clinical disease, which might evolve at any subsequent time throughout the span of life.

With the advent of antimicrobial drugs came the anticipation that we might be approaching a situation similar to that of syphilis, pneumococcic pneumonia, etc. It was hoped that the sulfones and, later, streptomycin, para-aminosalicylic acid and isoniazid, singly or in combination, might destroy tubercle bacilli in the human body. However, the fact that tuberculous lesions lose their blood supply dimmed the possibility of destroying tubercle bacilli except in fresh vascular areas of disease. Obviously, therefore, the only time that one might expect to cure tuberculosis with drugs in the sense of destroying all tubercle bacilli is reasonably soon after the initial invasion, while lesions are small and vascular.

Although lesions begin to form within an hour after the invasion, it is not known how soon their blood supply is lost. It has therefore been recommended by Waring and others that antituberculosis drugs be administered as soon as possible after the initial invasion occurs. Such invasions cannot be detected until the individual's tissues, including the skin, have become sensitized to tuberculoprotein. Sensitivity is rarely in evidence earlier than three weeks after the initial infection occurs, but can nearly always be elicited

by the tuberculin test within eight weeks. Thus, conversion of the skin to a state of sensitivity detectable only by the tuberculin reaction is the sole criterion for beginning the administration of drugs.

It is not yet known whether present antituberculosis drugs, singly or in combination, are capable of destroying all tubercle bacilli. However, considerable evidence has accrued to suggest that organisms are so suppressed that they are not likely to result in serious acute forms of the disease, such as meningitis, formerly seen in a small percentage of persons soon after sensitivity was established.

During the course of antituberculosis drug treatment, the only criterion by which its effectiveness might be determined is the reversion of skin sensitivity. There is some evidence that a constant supply of liberated tuberculoprotein is essential in the body to maintain sensitivity of tissues. Cases have already been reported in whom reversion of the tuberculin reaction has occurred during the course of antituberculosis drug treatment. It has not yet been determined whether all tubercle bacilli have actually been destroyed, or whether they have only been suppressed to such a low level that they are not multiplying and therefore tuberculoprotein is not available to maintain sensitivity.

If antituberculosis drugs only suppress tubercle bacilli to this low level, one may expect that after drugs are discontinued the organisms may later resume ability to multiply and liberate sufficient tuberculoprotein to sensitize the tissues again. This possibility must be considered, inasmuch as tubercle bacilli recovered from resected pulmonary lesions after long periods of drug treatment have immediately failed to produce disease in guinea pigs or to grow on culture medium. However, when incubated for several months, a considerable percentage has been found to resume multiplication.

Twenty years ago we had a large number of tuberculin converters on this campus, particularly in the Schools of Nursing and Medicine. In fact, in the Medical School class of 1936, 65% of those who entered uninfected became infected so as to react characteristically to tuberculin before graduation. We now have so few tuberculin converters that an adequate study of drug treatment among them with the hope of drawing dependable conclusions is not possible. However, in the small number to whom we have administered antimicrobial drugs, there are now two whose tuberculin sensitivity reverted after approximately one year of treatment.

Tuberculous Pleurisy with Effusion

Tuberculous pleurisy with effusion has been diagnosed in 115 persons. A considerable number of them were students of nursing and medicine, and the diagnosis was made soon after they became sensitized to tuberculoprotein. In others, effusions appeared in those who had long been known reactors to tuberculin.

The first symptom has usually been excruciating chest pain of sudden

onset, followed by fever. Rigler showed that 300 c.c. or more of fluid must be present in a pleural space before it is detectable on the usual postero-anterior x-ray film, but 100 c.c. may be found on films made in the lateral decubitus position. We have occasionally resorted to this technic when small effusions were suspected.

Throughout our 35 years of observation the term "idiopathic pleurisy with effusion" has been in vogue. Practically all such cases everywhere have been considered tuberculous. Finding tubercle bacilli in fluid has been our only incontrovertible diagnostic evidence. However, examination of fluid is often unrevealing, even though the condition is later found to be tuberculous. This is probably due to removal of an insufficient amount, or to the fact that the bacilli are so dilute that they are not found on direct examination. Even centrifuging a large volume of fluid and planting the sediment on culture medium or inoculating animals has sometimes failed.

Recently Stead et al. resorted to thoracotomy and biopsy in 24 persons hospitalized and under treatment for tuberculous pleurisy with effusion. Nine proved to be nontuberculous. With this more accurate diagnostic procedure now available, the term "idiopathic pleurisy with effusion" should be used with rarity in the future.

Treatment: The kind and length of treatment of these students have varied from none to most rigid and prolonged methods, including more than a year in sanatoriums. We have long recommended six months of bed-rest and another six months of graduated exercise, keeping the pleural space as dry as possible by aspiration as long as fluid formed. In recent years antituberculosis drugs have been administered for the entire 12 months.

Until recently the only method of preventing tuberculous pleurisy with effusion consisted of avoiding the initial invasion with tubercle bacilli. Now or in the near future it may be possible to destroy all tubercle bacilli in fresh primary lesions by antituberculosis drugs, thus preventing all clinical forms of tuberculosis.

Extrathoracic Tuberculosis

Since 1920 we have seen 61 persons with extrathoracic tuberculous lesions. Of this number, 23 had disease of *bones and joints,* some of which dated back to infancy and childhood. Among them were hunchback deformities and ankylosed hip joints. Others had been diagnosed sufficiently early and treated so promptly as to prevent crippling and deformity. Five with bone and joint disease had other demonstrable lesions. One with tuberculosis of the spine had pulmonary disease simultaneously. Another had pleurisy with effusion while the spine was involved. One with tuberculosis of a hip joint at the age of two years had had renal disease at the age of 21. One who had had disease of a hip joint as a child had had pulmonary tuberculosis at the age of 23 years. Another who had had hip joint disease at the age of nine had had cervical lymph node tuberculosis when he was 17 years old.

Renal tuberculosis was found in seven students. Although nephrectomy was considered when the disease was unilateral, two of these students were treated without surgery. One in 1927 had had bilateral lesions, and tubercle bacilli were found in urine from both ureters. She also had bilateral coexisting pulmonary disease. Both renal and pulmonary lesions responded well while she underwent a long course of bed-rest at home. There has since been no reactivation or new lesion. Another who had had tuberculosis of a hip joint at the age of two years had had unilateral renal tuberculosis when she was 21 years old in 1952. This apparently has been treated successfully with antituberculosis drugs, without surgery.

Cervical *lymph nodes* were involved in 22 of our students. Some had been treated successfully before entering school, and in others the nodes became involved while they were students. One who had had cervical nodes at the age of 18 years had had pulmonary tuberculosis at the age of 24. Another, a premedical student, had had cervical nodes detected in 1950 and a coexisting minimal pulmonary lesion. A third, who had had bilateral tuberculous cervical lymphadenitis in early childhood, had nephrectomy for renal tuberculosis while a sophomore, and tuberculous pleurisy with effusion while a senior in the University.

Since 1920 we have had only two cases of tuberculous *meningitis* in our clinic. One entered school at the age of 19 years in 1939. He reacted to tuberculin, which was the only evidence of the presence of tuberculosis. In 1941 he developed fatal tuberculous meningitis. The second, a man of 20 years, requested a tuberculin test on May 12, 1953, because of recent exposure to an aunt with contagious disease. He did not react. On July 20, 1953, he developed symptoms suggesting meningitis. He was hospitalized by his family physician. He then reacted to tuberculin, and acid-fast bacilli were recovered from spinal fluid. He was transferred to the State Sanatorium, where streptomycin, isoniazid and para-aminosalicylic acid were administered. Response was excellent and he was discharged in July, 1954. He returned to school in the fall of 1954 with no apparent residual, and has remained well. Antituberculosis drugs were continued until June, 1955.

One student had tuberculosis of the soft palate, two of the parotid gland; four had peritonitis, and one had a uterine tube involvement discovered during appendectomy.

Tuberculosis in Professional Schools

Although we had known of students of nursing and medicine who had fallen ill from tuberculosis, and of some who had died before the Students' Health Service was organized, the problem in these professional schools became more obvious soon after the chest clinic was established. While these schools constituted a small segment of the University's student body, they provided a preponderance of those with clinical tuberculosis.

Tuberculin testing of entering students in these schools quickly screened

out those who had not previously been infected with tubercle bacilli, and periodic testing of these individuals promptly identified those who became infected while in school. In the early 1930's it was found that the increment of infected students in the College of Education was about 1% per year, while that in the Schools of Nursing and Medicine was many times greater, particularly after the sophomore year.

An experiment had been set up for us without intention which was equal to any animal study that could have been devised. Both our nursing and medical students were being sent for instruction to a sanatorium for the tuberculous, where they had intimate contact with numerous contagious cases. Moreover, they were working in general hospitals which did not have tuberculosis services but were admitting patients for treatment of accurately diagnosed conditions such as diabetes and fractures, some of whom had unsuspected tuberculosis. In the late 1920's three other general hospitals operating schools of nursing were chosen on the basis of differing tuberculosis situations in order to round out our study on tuberculosis among students of nursing.

Periodic tuberculin testing of students who were uninfected before entering school uncovered important situations. For example, among those returning from a sanatorium service, a considerable number had become reactors. This was also true among those from certain services in general hospitals and institutions for the mentally ill. It was therefore possible to pinpoint the institutions—and often the departments—responsible for transmitting tubercle bacilli to students.

This experiment also provided an opportunity to study the evolution of tuberculosis in the adult human body. Periodic examinations of those who became infected on various services revealed that an occasional one soon had tuberculous pleurisy with effusion. In a few, primary pulmonary infiltrates were in evidence about the time sensitivity could first be elicited by the tuberculin test.

Continued observation of tuberculin converters, whether or not pleurisy with effusion or shadow-casting primary infiltrates had intervened, revealed that some of them later presented pulmonary and extrathoracic tuberculous clinical lesions. Such lesions did not all appear within one or two years after invasions with tubercle bacilli, but were spread over many years. These observations revealed the long, silent period that exists between the time lesions begin to cast shadows on x-ray films and the appearance of symptoms and abnormal physical signs.

The opinion that it is much more serious for primary tuberculous infections to be acquired in adulthood than in childhood was not substantiated. Students who became infected while in school and after graduation tolerated the invasions in the same way as those who had been infected as children. We have seen no difference in clinical lesions which subsequently developed as to severity or extent or response to treatment.

When it became obvious that many students were becoming infected with tubercle bacilli from patients with unsuspected tuberculosis in general hospitals, one of us (H. S. D.), on becoming Dean of Medical Sciences, University of Minnesota, in 1935, arranged to have all patients examined for tuberculosis on admission to University Hospital. He also provided for examination of hospital personnel, both preëmployment and semi-annually. This program proved so effective that it has since been in continuous operation. It has now been adopted by all general hospitals in Minneapolis and St. Paul.

Early in the 1930's, contagious disease technic was instituted on a small tuberculosis service at the University Hospital. This is now employed in practically all general hospitals in this vicinity.

For a number of years our students of medicine spent two weeks in residence in a sanatorium in intimate contact with contagious patients. However, testing with tuberculin before and after this service revealed such a large number of converters that the students protested and this service was discontinued in 1936. Later a tuberculosis service operated under strict contagious disease technic was substituted.

The effectiveness of these methods of controlling tuberculosis among students of nursing and medicine has been almost phenomenal. For example, in the School of Medicine a survey reported in 1941 on the classes being graduated from 1919 to 1932, inclusive, revealed that 92 (7.1%) had developed demonstrable tuberculous lesions while in school or after graduation, and that 11 of them had died from tuberculosis. A recent survey revealed that in the past 14 years only one student developed a clinical lesion large enough to be detected by its x-ray shadow. He had been infected before entering the School of Medicine.

In one school of nursing, from 12 to 19% of students developed demonstrable tuberculous lesions before graduation prior to the institution of this program. Since it has been well established, only four have developed clinical disease, all of whom had been infected before entering school.

Tuberculosis on the Campus as a Whole

Since 1920, students entering the University of Minnesota have been given complete conventional physical examinations. However, it was not unusual to see individuals whose disease had been missed by the entrance examination present symptoms such as hemorrhage due to extensive chronic pulmonary tuberculosis during the freshman year.

At that time, and for a few years thereafter, to add chest x-ray inspection to the entrance examination was out of the question because: (1) the majority of physicians still believed that all tuberculosis could be found by symptoms and physical signs; (2) the cost of x-ray film work was prohibitive in such large numbers; (3) our x-ray department was not equipped for such a volume of work.

The tuberculin test was practically ignored except for those who presented evidence of gross disease or were ill. We were laboring under the old teaching that in early adult life nearly everyone had been infected with tubercle bacilli and therefore would react.

To test the validity of former teachings, the tuberculin test was administered by the epidermal method (Pirquet) to our entering students in the fall of 1928. Only about one in three reacted (figure 1). When published, this report was questioned on the ground that the intracutaneous method of administration (Mantoux) is more accurate and would have given a higher yield. In the fall of 1929, the entering students received tuberculin by this method, but with a slightly lower percentage of reactors than in 1928.

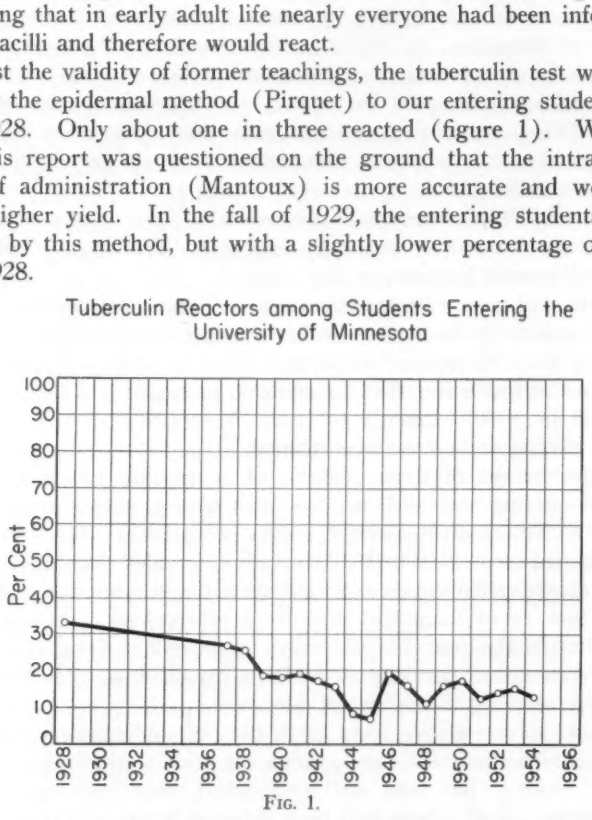


FIG. 1.

Ghon had already demonstrated that, in persons who had no evidence of tuberculosis during life except the tuberculin reaction, lesions could always be found at necropsy. It was later shown that such lesions contain living tubercle bacilli. Therefore, a tuberculin reaction demonstrates the presence of tubercle bacilli in the individual's body as certainly as though these organisms were seen under the microscope or were grown in culture medium or in experimental animals.

It was also known that the tuberculin test detects the presence of tuberculosis after an invasion with tubercle bacilli occurs far earlier than any other phase of examination. Usually within three to seven weeks the body tissues, including the skin, are so sensitized to tuberculoprotein as to react characteristically to tuberculin. In the vast majority of cases this is long before x-ray inspection of the chest, symptoms, conventional physical signs, etc., are of avail.

It was observed that only persons who are invaded with tubercle bacilli and soon become tuberculin reactors may later develop clinical tuberculous lesions. We therefore recognized the tuberculin test as our most effective weapon against the tubercle bacillus. It not only told us in whose bodies they had found refuge, but also that those persons should be promptly examined for clinical disease and, if this was not found, should be periodically examined for that which might subsequently evolve. Moreover, it told us that the reactor had been in contact with a contagious person who should be sought and managed.

Obviously our problem lay in those who reacted to tuberculin on entrance to school and those who became reactors while in school. Since only one third of the students harbored tubercle bacilli on admission, at that moment it was only they who constituted a tuberculosis problem.

In 1929 fluoroscopic inspection of the chest became a part of the examination of entering students. This resulted in our finding between three and four times as many cases of tuberculosis as previously, when only conventional physical examination was made.

So much evidence had accrued pertaining to the value of x-ray film inspection of the chest that one of us (H. S. D.), Director of the Students' Health Service, was thoroughly convinced that it should become a requirement for every entering student who reacted to tuberculin. This was approved by the President of the University, and in the fall of 1931 all entering reactors had chest x-ray film inspection. In that class, 22 were found to have clinically important tuberculous pulmonary infiltrations. One, who had been a high school athlete the year before and had no symptom on admission, had far advanced contagious tuberculosis. Five had moderately advanced disease, and the remainder had minimal lesions. Since that time, students who react to tuberculin on admission have had chest x-ray film inspections.

In 1932 one of us (H. S. D.) wrote concerning the beginning of this program as follows: "It would be possible, by extending such a program to the entire student body or to any other group of individuals, to diagnose all tuberculosis in its truly curable stage and to prevent individuals in the group from transmitting the infection to their associates."

We have sought to protect students by managing tuberculosis as a contagious disease. On numerous occasions, outside pressure has been exerted for the use of one or more of the various agents recommended for immunization. Inasmuch as a mild or severe attack of tuberculosis has never been found to leave the human body dependably immunized, there appeared no premise for attempting to produce immunity artificially. At no time was incontrovertible evidence adduced anywhere for the efficacy of so-called immunizing agents. Moreover, we were fearful of living tubercle bacilli, regardless of low degree of virulence at the time, because of the possibility of mutation occurring in the culture medium and in the human body. This

fear has been justified by numerous clinical lesions, and even death reported to have been caused by Bacillus Calmette-Guerin. To have artificially sensitized the tissues of students would have completely destroyed the numerous values of the tuberculin test, which has proved to be the master key in every phase of our work.

Personnel: Apparently it has been difficult in many colleges and universities to procure coöperation in extending the tuberculosis control program to personnel. This is unfortunate, because more clinical and contagious tuberculosis develops among persons in the older age bracket than among those of student age.

On this campus, cases of contagious tuberculosis were known to exist among faculty members. Some students who developed tuberculosis maintained that they had contracted it from their teachers. All attempts to control this situation failed until the spring of 1938, when one of us (R. E. B.) succeeded in having a ruling made by the Board of Regents that all new nonacademic employees in the University should be required to have a physical examination before such employment. Physical examinations of all new members of the academic staff and those promoted to positions implying tenure have been required since the spring of 1941. The Health Service has conducted these examinations with the same completeness as those of students.

As the percentage of tuberculin reactors on admission increased or decreased, the tuberculosis problem on the campus varied accordingly, inasmuch as every reactor is a potential case of clinical disease. Figure 1 shows that approximately 33% of students entering the University of Minnesota in 1928 were already harboring tubercle bacilli. Over the succeeding years there was a decrease until 1945, when only 6.4% reacted. The next year a large number of entering students had recently returned from military service, many having been in countries where little has been done to control tuberculosis. With this influx, 19.3% of all entering students reacted in the school year 1946 and 1947. As the number of war veterans decreased, there was a corresponding reduction of tuberculin reactors among entering students. However, this percentage has since fluctuated, due to such factors as the Korean war and other military service, as well as increase in number of students from other countries.

During the last few years we have had a sizable number of students from other countries, mostly for graduate work, a high percentage of whom were tuberculin reactors on admission. For example, among the 355 who entered for the year 1953–54, 68.7% reacted to tuberculin, whereas among the entire entering student body of 5,509 that year, only 15.4% reacted. Wherever there is a high incidence of infection there is a correspondingly high morbidity rate. During the last six years 25 students have had diagnoses of clinical pulmonary tuberculosis first made on entrance or while in school of whom 15 (60%) were from other countries, despite the fact

that such students constituted only approximately 2.5% of the student body.

The program of managing tuberculosis on this campus over the last 35 years has resulted in a state of control that was beyond our fondest hopes in 1920. It has been so standardized as to be applicable in colleges and universities everywhere.

Summary and Conclusions

1. A chest disease clinic has been in continuous operation at the Students' Health Service, University of Minnesota, since 1920. From the 155,021 students who have enrolled and the personnel, 7,530 have been examined in this clinic.

2. Tuberculosis has been the most prevalent major disease on the campus, from the standpoint of both incidence of infection and clinical lesions. We have had under observation and care 1,055 persons with pulmonary tuberculosis, 115 with tuberculous pleurisy with effusion, and 61 with extrathoracic lesions.

3. Diagnostic procedures have ranged from conventional physical examination, x-ray film inspection, and bacteriology of sputum and gastric washings, to thoracotomy and pulmonary biopsy.

4. The most serious problems were in the Schools of Nursing and Medicine. In these the situation was such as to constitute a natural experiment from which information was gained concerning the evolution of tuberculosis from the time of first invasion with tubercle bacilli in adults through the various stages of development of the disease.

5. It was observed that first infections acquired by adults behave in the same manner as those which occur in children.

6. The tuberculin reaction was in evidence within a few weeks after invasions of tubercle bacilli occurred. This reaction detected the presence of primary tuberculosis earlier than any other phase of the examination.

7. Only tuberculin reactors later developed clinical disease. Periodic examinations of reactors detected clinical lesions when minimal and while in presymptom and precontagious stages.

8. The tuberculin test has been routinely administered to all students entering the University since 1928.

9. The incidence of tuberculin reactors markedly increased in 1946, due in part to the return of a large number of war veterans from parts of the world where tuberculosis is still rife. Although the incidence again decreased, it has fluctuated, probably because of those later in military service, including the Korean war, as well as a sizable number of students from other countries on the campus.

10. While many of our students have been subjected to exposure to tubercle bacilli in military service since 1940, those who became infected presented tuberculosis problems no different from those we have observed among the students who became infected in childhood.

11. X-ray film inspection of the chests of reactors became routine in 1931. Shadows seen on x-ray films were not pathognomonic. Nevertheless, they often located areas of disease when other phases of the examination failed. Knowing that gross lesions were present by the shadows they cast, we found it was usually possible to determine etiology by other methods.

12. Clear chest x-ray films never proved absence of tuberculosis. To cast shadows, lesions must be macroscopic and must have sufficient consistency to obstruct x-rays. Such lesions must also be in the 75% of the lungs visualized on x-ray films. These facts were established from postmortem and resected pulmonary units. Special technics have been employed, including planigraphy.

13. Treatment has ranged from conventional bed-rest and pulmonary collapse to antituberculosis drugs and resectional surgery.

14. Primary pulmonary tuberculous infiltrates resolved regardless of how much or how little treatment was administered. No case of immediately progressive primary pulmonary tuberculosis has been seen.

15. Antituberculosis drugs have been administered to a few tuberculin converters in recent years. Two reverted to nonreactors after one year of treatment. Whether these drugs are germicidal in such cases is not yet known.

16. Prevention has consisted of managing tuberculosis as a contagious disease. Since a mild or severe attack does not result in dependable immunity, we found no premise for attempting to produce immunity artificially.

17. In 1935, plans were made for examination for tuberculosis of all patients admitted to the University Hospital and for preëmployment and semiannual examinations of all hospital personnel. This program has since been in continuous operation.

18. Since the early 1930's rigid contagious disease technic has been employed in the care of tuberculous patients in the University Hospital.

19. Tuberculosis was a serious problem among University personnel until 1938, when the Board of Regents passed a ruling requiring examination of nonacademic and, in 1941, of academic employees.

20. The accomplishments of the tuberculosis control program on this campus have been phenomenal. Students no longer die from tuberculosis, and morbidity has been reduced to a trickle. In the School of Medicine, where in the classes of 1919 to 1932 11 died and 92 developed demonstrable tuberculous lesions, only one in the past 14 years has presented a lesion large enough to cast a visible shadow.

ACKNOWLEDGMENT

We are especially indebted to Mrs. Eleanor Sundstrom, Mrs. Kaye Swedien and Mr. Paul Rupprecht for their participation in assembling, tabulating and analyzing data.

SUMMARIO IN INTERLINGUA

Ab 1920 a 1955, 7.530 individuos inter le 155.021 studentes e le empleatos del Universitate Minnesota recipeva examines special al clinica thoracic. In 1.055,

tuberculose pulmonar esseva constatate; 115 habeva pleuritis tuberculotic con effusion; e 61 habeva tuberculose extrathoracic.

Le test a tuberculina se provava le melior agente diagnostic e epidemiologic. Illo etiam determinava le dimensiones del problema de tuberculose e provideva le melior information relative al efficacia del mesuras therapeutic. Depost 1928, nove studentes recipe le test a tuberculina, e le individuos con reaction positive es subjicite a un examine roentgenologic del thorace. In le Schola pro Infirmeras e le Schola Medical (ubi le problema esseva le plus serie), individuos in qui le test a tuberculina esseva positive al tempore de lor admission esseva subjicite a examines roentgenologic del thorace a intervallos de sex menses. Iste methodo resultava in le discoperta de evolvente chronic lesiones pulmonar durante le phase pre-symptomatic e pre-contagiose e provideva informationes relative al effectos del therapia.

Semiannual tests a tuberculina pro individuos con reactiones negative rendeva possibile le detection del presentia de tuberculose ante que le roentgenogramma poteva revelar ulle umbra e usualmente a un tempore quando le lesiones esseva ancora microscopic. Studentes in qui le reaction a tuberculina deveniva positive durante lor sojorno al schola recipeva re-inspectiones roentgenologic del thorace a intervallos regular de sex menses. Lesiones que esseva satis grande e dense e que esseva locate de maniera a resultar in visibile umbras roentgenologic al tempore del declaration del allergia esseva recognoscite como infiltratos primari (tuberculos de Ghon in le stadio inflammatori).

Esseva trovate nulle supporto pro le supposition que infectiones tuberculotic acquirite al etate adulte es plus serie que tal infectiones acquirite durante le infantia. Illos se resolve lentemente in adultos, exactemente como in juveniles.

Le methodos de proteger le studentes contra bacillos tuberculotic consisteva in tractar tuberculose como un morbo contagiose; rigide technicas pro morbos contagiose esseva instituite ubicunque patientes tuberculotic esseva examinate e tractate. Depost 1935, omne individuos admittite al hospital ha essite examinate pro tuberculose, e le technicas appropriate esseva usate in casos in que ille morbo esseva detegite.

Proque ni un leve ni un sever attacco de tuberculose pote garantir le disveloppamento de immunitate contra attaccos subsequente, nos non vide ulle justification pro tentar le production de immunitate artificial. In ultra, nos reguarda como riscose omne administration de vive bacillos tuberculotic—sin reguardo a si o non lor virulentia es reducite—proque il existe le possibilitate del apparition de mutantes que pote causar lesiones clinic.

Le resultatos obtenite per nostre methodos esseva phenomenal. In le Schola Medical, 92 individuos disveloppava lesiones demonstrabile e 11 moriva in le classes terminante lor cursos ab 1919 a 1952, sed non plus que un sol studente ha disveloppate un lesion satis grande pro esser detegite per medios roentgenologic in le curso del passate 14 annos. In le Schola pro Infirmeras, le resultatos esseva equalmente bon.

DIAGNOSIS OF ARTERIOSCLEROTIC ANEURYSMS OF THE THORACIC AORTA: REPORT OF SIX CASES * †

By Israel Steinberg, M.D., F.A.C.P., *New York, N. Y.*

In recent years, more and more aneurysms of the thoracic aorta have been due to arteriosclerosis. This is because the incidence of cardiovascular syphilis is declining while longevity is increasing.[1] Heretofore, discovery of aortic aneurysms was mostly of academic interest; wiring and cellophane wrapping having been of limited success. Newer surgical technics, especially excision of the aneurysm and replacement with homologous aortic grafts, promise to be a more effective treatment.[2, 3]

The early diagnosis of thoracic aortic aneurysm is important; duration of life, once symptoms begin, is apparently limited.[4, 5] Roentgenography fortunately provides a significant clue by disclosing abnormal mediastinal or hilar shadows. If the vascular nature of the lesions is obscure, contrast visualization of the thoracic aorta by the method of angiocardiography will readily establish the diagnosis.[6] This report is concerned with the diagnosis and clinical features during life of arteriosclerotic thoracic aortic aneurysms in six patients.

Case Reports

Case 1. Recurrent Laryngeal Nerve Paresis, Saccular Aneurysm Aortic Arch and Sudden Death Within One Year. A 51 year old truckman was referred by Dr. Murray J. Pokress on December 27, 1954, complaining of hoarseness of three weeks' duration. Six weeks earlier he had experienced severe, viselike epigastric pain radiating to the back. He was suspected of having a peptic ulcer; gastrointestinal x-rays were made and found to show deformity of the duodenum. Subsequently, on a diet, he had subsidence of pain but noted hoarseness. He consulted a nose and throat specialist, who obtained chest x-rays; these disclosed a mediastinal mass.

Physical examination revealed a well developed and nourished man in no discomfort. Hoarseness was present and became aggravated by movement of the head towards the left. Indirect laryngoscopy revealed decreased left vocal cord movement. The neck vessels were pulsatile. The apex beat of the heart was heaving in character; murmurs were not present. The pulses were equal and regular; the blood pressure was 140/90 mm. of Hg. The wrist arteries were tortuous and sclerotic; the leg vessels were palpable. Abdominal examination revealed no masses; calcium in the abdominal aorta was not detected on x-ray examination. Fluoroscopic and roentgenographic studies of the chest (figure 1A) revealed a nonpulsatile mass

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From the Departments of Medicine and Radiology, The New York Hospital-Cornell Medical Center.

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Requests for reprints should be addressed to Israel Steinberg, M.D., 170 East Seventy-seventh Street, New York 21, N. Y.

measuring 4 cm. in diameter adjacent to the aortic knob. The heart was not enlarged; the descending aorta appeared dilated, dense and tortuous (figure 1B). The electrocardiographic examination was normal and the blood Wassermann test was negative.

Angiocardiography (figure 1C) revealed a normal left ventricle. The ascending aorta was also normal in size and configuration, the diameter of the mid ascending portion being 30 mm. (average normal, 28 mm.). The transverse portion was dilated (diameter, 35 mm.), and contained an aneurysm measuring 45 mm. in



FIG. 1. *Case 1.* Arteriosclerotic saccular aneurysm, aortic arch, causing recurrent laryngeal nerve paralysis and hoarseness. A. Conventional frontal x-ray. Arrow points to left mediastinal mass.

diameter. Following the aneurysm at a distance of 3 cm., the descending aorta again became dilated (measuring 50 mm.) and then tapered to a diameter of 30 mm. The posterior wall of the descending aorta showed thickening varying from 7 to 10 mm. (average normal aortic wall thickness, 2 mm.).

Nine months later, on September 21, 1955, the patient had sudden onset of severe right lower abdominal pain. He was rushed to another hospital and found to be pale, sweating, anxious and in shock. The abdomen was soft, without spasm, diffusely tender and contained a fluid wave. Laboratory studies showed: hemoglobin, 13.7 gm./100 c.c.; erythrocytes, 4.7 m./cu. mm.; leukocytes, 11.250, with 70% poly-

morphonuclears. In a few hours, despite blood transfusion, he had further distention of the abdomen and became comatose. The hemoglobin fell to 5.8 gm./100 c.c.; death occurred within 24 hours of onset of symptoms.

Case 2. Hypertension, Mitral Stenosis, Hemoptysis, Saccular Aneurysm Aortic Arch with Left Pulmonary Artery Stenosis. A 65 year old housewife, referred by Dr. Elliot Hochstein, was admitted on July 5, 1955, with high blood pressure and hemoptysis. Hypertension had been discovered following delivery, 30 years prior to the present admission. The hypertension had been asymptomatic despite chronic

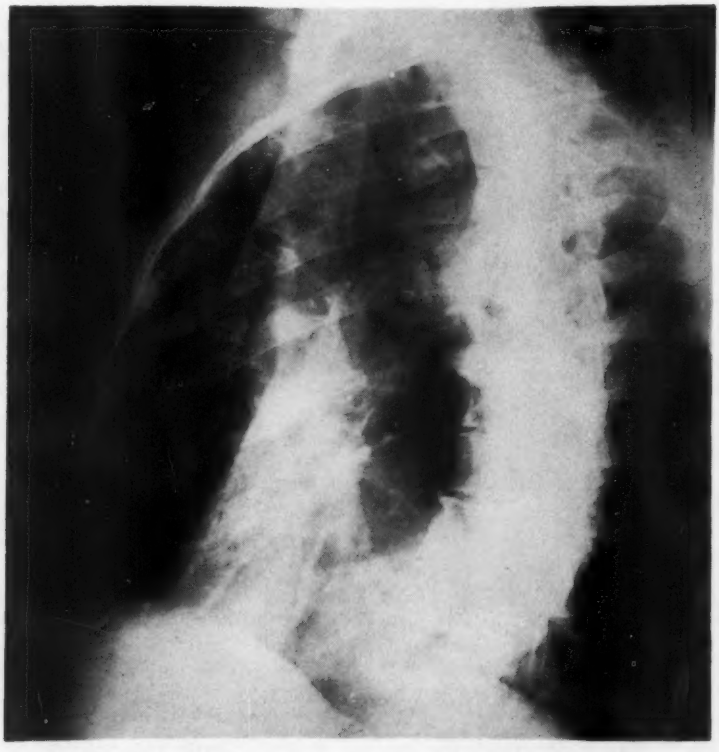


FIG. 1B. Conventional left anterior oblique view shows enlargement and tortuosity of the descending thoracic aorta.

cholecystitis, cholelithiasis and cholecystectomy; the blood pressure had averaged 150/90 mm. of Hg. Following operation in 1951, headaches occurred which were not relieved by Serpasil and Apresoline. In recent years the blood pressure had increased to an average of 220/120 mm. of Hg. Nine months prior to admission, pressing substernal sensations began which were relieved by the expectoration of blood tinged sputum. On the day of admission a small hemoptysis had occurred; roentgen study of the thorax disclosed a left hilar mass.

Physical examination showed the patient to be well developed and nourished. The heart was enlarged 2 cm. outside the left midclavicular line. A presystolic

murmur was heard at the apex. The blood pressure was 210/170 mm. of Hg; the pulse was regular. Serologic test of the blood for syphilis was negative. The electrocardiogram showed right bundle branch block (QRS, 0.15 sec).

In 1951 a chest x-ray had shown an enlarged heart; the aorta was normal except for calcium plaques in the knob. In 1955 (figure 2A) a mass had developed which also contained calcium adjacent to the aortic knob. Angiocardiography revealed an



FIG. 1C. Left anterior oblique angiocardiogram reveals a normal left atrium and ventricle. The ascending aorta is also normal in size and contour. Note the saccular aneurysm of the transverse aorta (arrows), followed by the normal descending aorta, which becomes tortuous and dilated in the lower portion and contains a thickened posterior wall (arrow).

enlarged right ventricle, pulmonary artery and right branch; the left pulmonary artery appeared narrowed (figure 2B). When the left side of the heart was opacified (figure 2C), there was unfolding of the aorta and a saccular aneurysm surrounded by thrombus adjacent to the aortic knob. The left anterior oblique angiocardiogram also revealed enlargement of the left atrium and ventricle; the ascending aorta appeared moderately dilated (diameter, 45 mm.) but was smooth in outline. A sac-

cular aneurysm was seen just beyond the origin of the left subclavian artery. The descending aorta was irregular in outline but remained undilated (figure 2D).

Following discharge, Serpasil and Ansolysen were prescribed. Since then the blood pressure has averaged 170/90 mm. of Hg. Hemoptysis has not recurred; roentgen examination of the aorta has remained unchanged.

Case 3. Fusiform Aneurysm of Arch, Sudden Death After Femur Nailing Operation. A 69 year old woman, referred by Dr. Carl Muschenheim on April 11, 1955, complained of pain in the left chest and back of six months' duration. The

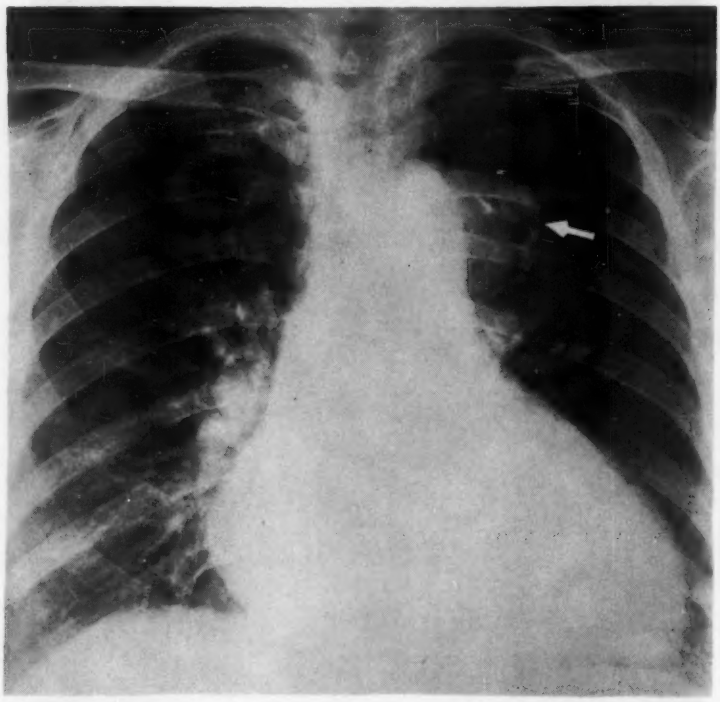


FIG. 2. *Case 2.* Arteriosclerotic saccular aneurysm, aortic arch, associated with hypertension and mitral stenosis. A. Conventional frontal roentgenogram shows enlargement of the heart and a large left mediastinal mass containing calcium plaques (arrow). The aortic knob also contains calcifications.

only previous illness was an ovarian carcinoma which had been treated by subtotal hysterectomy and x-radiation 27 years earlier. The patient had been followed regularly in another hospital and had been well except for recurrent cystitis. Back pain radiating along the thoracic spine and fifth and sixth ribs had only recently occurred. Chest roentgenograms disclosed a mediastinal mass.

Physical examination revealed a well developed and nourished woman in no distress. No abnormality of the heart, lung, bones or abdomen was found. The blood pressure was 150/90 mm. of Hg. The electrocardiogram was normal. The Mazzini test was negative. X-ray examination of the chest revealed a left mediastinal

mass (figure 3A). In the left anterior oblique view (figure 3B), the transverse aorta was dilated and contained linear calcifications. The frontal angiocardiogram revealed a tortuous, slightly dilated ascending aorta with a markedly deformed transverse aorta which contained a thick thrombus along the left border (figure 3C). The left anterior oblique angiocardiogram revealed a smooth, somewhat dilated ascending aorta which measured 37 mm. in the mid-ascending portion. A huge



FIG. 2B. Frontal angiocardiogram shows marked right ventricular enlargement, enlargement of the pulmonary artery and left branch. The left pulmonary artery is constricted (arrow) by the aortic aneurysm.

fusiform aneurysm containing calcium in its wall was located at the origin of the left subclavian artery. The descending aorta was tortuous and somewhat irregular (figure 3D).

On May 11, 1955, the patient was admitted to another hospital. In addition to the aortic aneurysm, osteoarthritis of the spine and general osteoporosis of the skeleton were found. An isolated osteolytic lesion of the left femur was suspected. On May 12, 1955, a biopsy of the left femur was done, and pathologic study showed

fibrous walled cystic structures. The patient made an uneventful recovery, but a month later fell and fractured the left femur at the site of biopsy. A nailing operation was done, June 16, 1955; subsequently, the patient did well but eight days later died suddenly. Permission for autopsy was not secured.

Case 4. Fusiform Aneurysm Descending Thoracic Aorta Eroding Dorsal Spine. Thrombosis of Unsuspected Abdominal Aneurysm Following Excision and Grafting of Thoracic Aneurysm; Excision and Grafting of Abdominal Aneurysm; Kidney

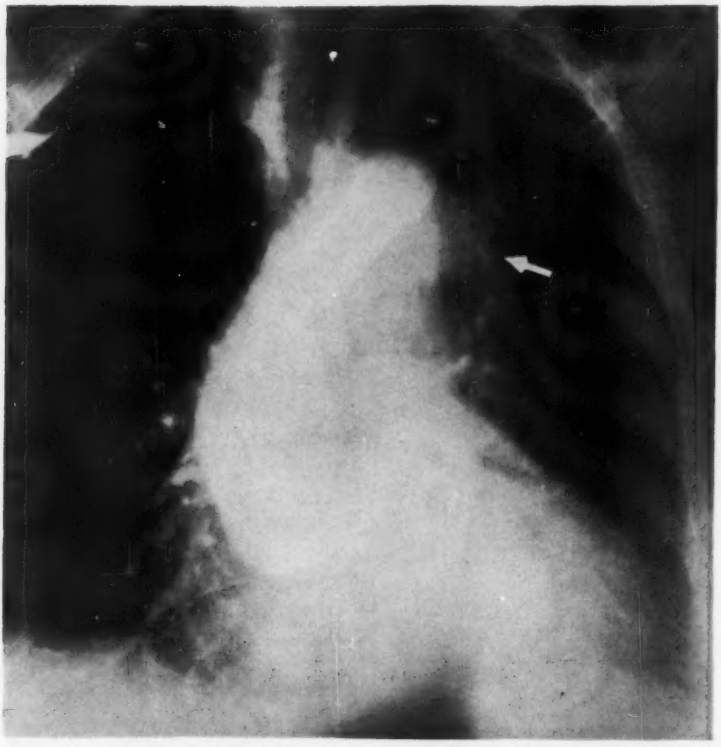


FIG. 2C. Frontal angiocardiogram shows some enlargement of the left ventricle and uncoiling of the aorta. Note the saccular aneurysm with surrounding thrombus (arrow) adjacent to the origin of the descending aorta.

Failure. A 57 year old white telephone executive, referred by Dr. Aaron Feder, was admitted on October 19, 1955, complaining of back pain of three months' duration. Hypertension had been discovered during a routine physical examination five years prior to admission. He had been put on a reducing low fat and salt-free diet, sedatives and hypotensive drugs. Following this he had lost 20 pounds and had been asymptomatic. Suddenly, three months prior to admission, attacks of severe sharp pain located in the left scapular area began and were relieved by resting and leaning forward. Three weeks prior to admission, chest x-rays disclosed a mass and he was sent into the hospital for study.

Physical examination revealed a well developed and nourished man. The abdomen was muscular; no masses or pulsations were felt. Indeed, the only abnormal finding was hypertension (220/106 mm. of Hg). Laboratory studies, including blood and spinal fluid Wassermann tests, were negative. Chest x-rays (figures 4A and B) showed a huge, nonpulsatile, rounded posterior mediastinal mass in the region of the mid-dorsal spine. Below the mass there was forward angulation of the



FIG. 2D. Left oblique angiocardiogram shows some dilatation of the midportion of the ascending aorta, which, however, is regular in contour. A saccular aneurysm (arrow) arises high in the descending aorta; below, the aorta is normal.

esophagus (figure 4B). Angiocardiography (figures 4C and D) revealed a smooth, normal ascending aorta (diameter, 35 mm.) and a normal aortic arch. A fusiform aneurysm of the mid-descending aorta, surrounded by thrombus along its left border and measuring 55 cm. in diameter, was visualized. Dilatation of the remaining descending aorta was also present (figure 4D), and was responsible for the anterior displacement of the esophagus. Subsequently, tomographic studies of the thoracic vertebrae showed mild erosion of the anterior bodies of the fifth and sixth thoracic

vertebrae. Abdominal films failed to reveal calcification in the aorta or branches. Electrocardiographic studies showed only left axis deviation.

On January 27, 1956, Dr. M. E. DeBakey * operated on the patient, utilizing general endotracheal anesthesia and general body hypothermia (rectal temperature, 86° F.). The left pleural cavity was entered and exploration revealed the aortic aneurysm (figure 4E). The aneurysm was thin and fusiform in character, and measured approximately 9 cm. in greatest diameter. Following complete mobilization of the aorta, occluding clamps were placed above and below the aneurysm, which

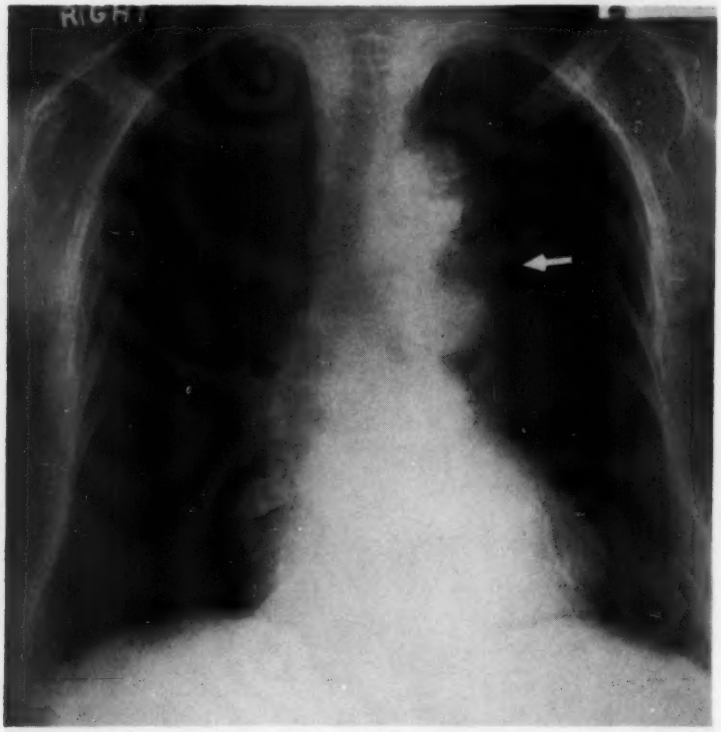


FIG. 3. *Case 3.* Arteriosclerotic fusiform aneurysm of the aortic arch. A. Conventional frontal x-ray shows a deformed aortic arch with a left mediastinal mass (arrow).

was then isolated and excised. The aortic defect was bridged by an aortic homograft and a good pulsatile blood flow was obtained after release of the clamps. The total aortic occlusion period was 36 minutes.

Rewarming began with closure of the wound, and within two hours the body temperature was restored to normal. When the rubber blanket used in the rewarming procedure was removed, circulation through the lower extremities was found blocked, femoral and leg pulses being absent. A saddle embolus at the bifurcation of the abdominal aorta was suspected, and immediate peritoneal cavity incision and

* Operation and autopsy findings, courtesy Dr. M. E. DeBakey.

exploration of the aorta were made. A fusiform aneurysm extending from the renal arteries to the aortic bifurcation into the iliac vessels was discovered; lower iliac artery pulsations were absent. Further examination revealed thrombosis of the abdominal aneurysm, apparently the result of the clamping of the thoracic aorta during operation. The abdominal aortic aneurysm was mobilized, freed of surrounding structures and excised. A good retrograde flow of blood through the aorta from below the bifurcation was found. Accordingly, a homograft was used to bridge



FIG. 3B. Conventional left anterior oblique view shows a markedly dilated transverse aorta containing calcium (arrows).

the gap. The occlusion time for the abdominal aorta was 41 minutes, the total operation time being 90 minutes.

The patient tolerated both operative procedures well and without shock; the immediate postoperative recovery was also satisfactory. However, the urinary output was only 90 c.c. in the next 24 hours. After five days of meager urinary output, dialysis with an artificial kidney apparatus was begun, but it failed to restore kidney function. Death occurred suddenly on the eighth postoperative day.

The resected abdominal aortic aneurysm showed a fresh thrombus blocking the

lumen of the abdominal aorta at the bifurcation. Old thrombus in layered fashion but with a free central channel was present in the excised abdominal aorta aneurysm. At necropsy, the kidneys showed the changes of lower nephron nephrosis. The homografts in the thoracic and abdominal aorta were intact and free of thrombosis.

Case 5. Multiple Fusiform Aneurysms of Thoracic Aorta in an Asymptomatic 77 Year Old Woman. A 77 year old housewife was referred by Dr. Robert Wallach on December 29, 1955. There were no symptoms referable to the thorax. During the last two years there had been weakness, an unsteady gait and easy fatigability.

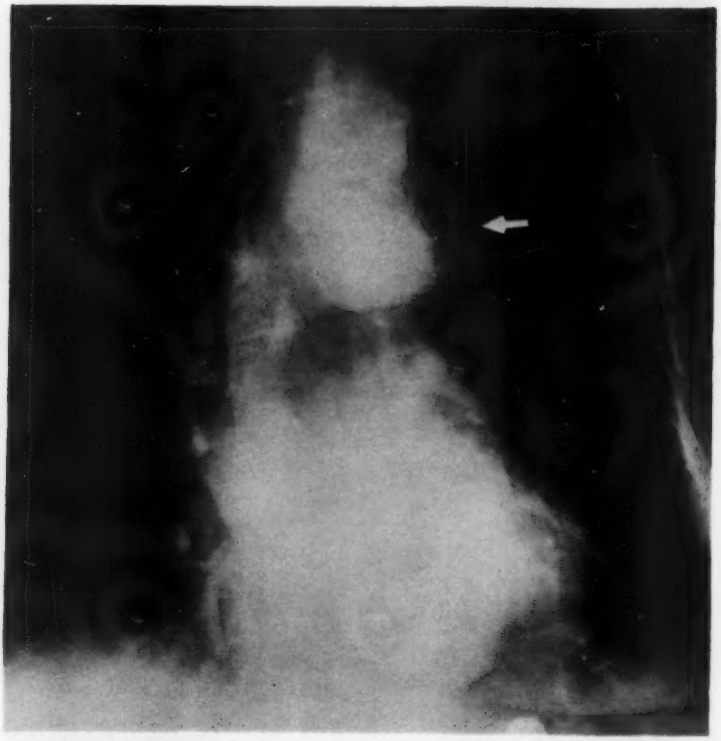


FIG. 3C. Frontal angiocardiogram shows a smooth, normal sized ascending aorta with distorted transverse and descending portions. Note the thrombus (arrow) along the left side of the descending aorta.

Her doctor had been consulted because of mild nausea, which subsequently subsided. Routine chest fluoroscopy, however, disclosed mediastinal and hilar masses. The patient had no knowledge of hypertension; indeed, the only previous illness had been intestinal obstruction five years earlier, which had been completely relieved by operation.

Physical examination revealed a well developed and nourished woman in no discomfort. The heart did not appear enlarged. There was a high pitched (grade 4) systolic murmur at the apex and base of the heart. The peripheral arteries were tortuous and calcific. The blood pressure was 160/110 mm. of Hg right arm; 120/90

mm. of Hg left arm. Electrocardiographic examination revealed left axis deviation and occasional ventricular premature beats. Fluoroscopic and x-ray examination of the chest (figure 5A) revealed a nonpulsatile mass above the aortic arch. The descending aorta was tortuous and markedly enlarged. Angiocardiography (figure 5B) showed a slightly enlarged left ventricle; the ascending aorta appeared smooth



FIG. 3D. Left anterior oblique angiocardiogram. Note the huge, fusiform aneurysm of the transverse aorta.

in outline; the diameter of the mid-ascending portion measured 37 mm. There was marked tortuosity of the brachiocephalic arteries, and just beyond the origin of the left subclavian artery the aortic arch became diffusely dilated (50 mm. in diameter) for a distance of 8.5 cm. and contained a huge, laminated thrombus extending toward the apex of the lung. Distalward, the descending aorta became tortuous (diameter, 35 mm.), and again in the lower thorax it became aneurysmal with a large thrombus.

Case 6. Hypertension, Fusiform Aneurysm Descending Aorta; Pulmonary Fibrosis and Emphysema. A 61 year old white garage man, referred by Dr. Raymond Miller, was admitted on January 15, 1956, with chief complaint of dyspnea of five years' duration. Several years prior to admission he had consulted a physician because of obesity, and hypertension had been discovered. He had been put on a rice diet, had lost 16 pounds and had remained well until he began having dyspnea. This gradually increased and was associated with cough, expectoration and wheezing.

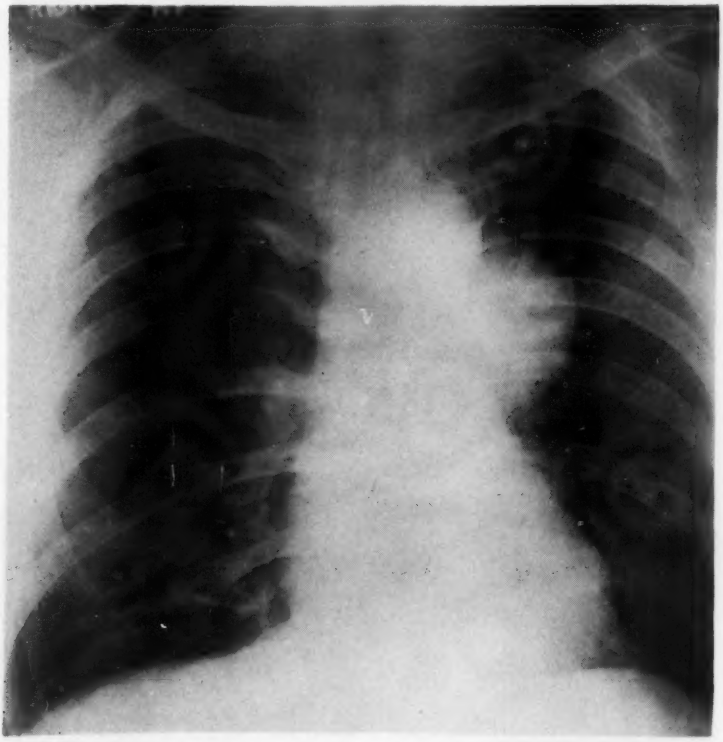


FIG. 4. *Case 4.* Arteriosclerotic fusiform aneurysm of the descending aorta associated with hypertension. A. Conventional roentgenogram showing a huge, rounded left hilar mass.

Physical examination revealed a well developed and nourished man. The chest was barrel-shaped and hyperresonant. The breath sounds were diminished; there were no râles. The heart was not enlarged. A loud, harsh (grade 4) systolic murmur was heard at the apex and transmitted along the left sternal border. The blood pressure was 145/92 mm. of Hg. The dorsalis pedis and posterior tibial arteries were not palpable, and the femoral pulsations were weak. No masses were felt in the abdomen. Indirect laryngoscopy showed slight delay in closure of the left vocal cord. Electrocardiographic examination revealed a P-R interval of 0.21 sec. and left axis deviation. The Wassermann blood test was negative.

Roentgenographic studies of the chest disclosed generalized mottling of the

lungs. The heart was slightly enlarged, and a pulsatile, enormously enlarged descending aorta was present (figure 6A). Comparison with a film made a year earlier showed that the descending aorta had increased in size. Angiocardiography (figures 6B and C) showed a huge fusiform aneurysm of the descending aorta. The frontal angiocardiogram (figure 6B) showed thrombus lining the posterior wall.

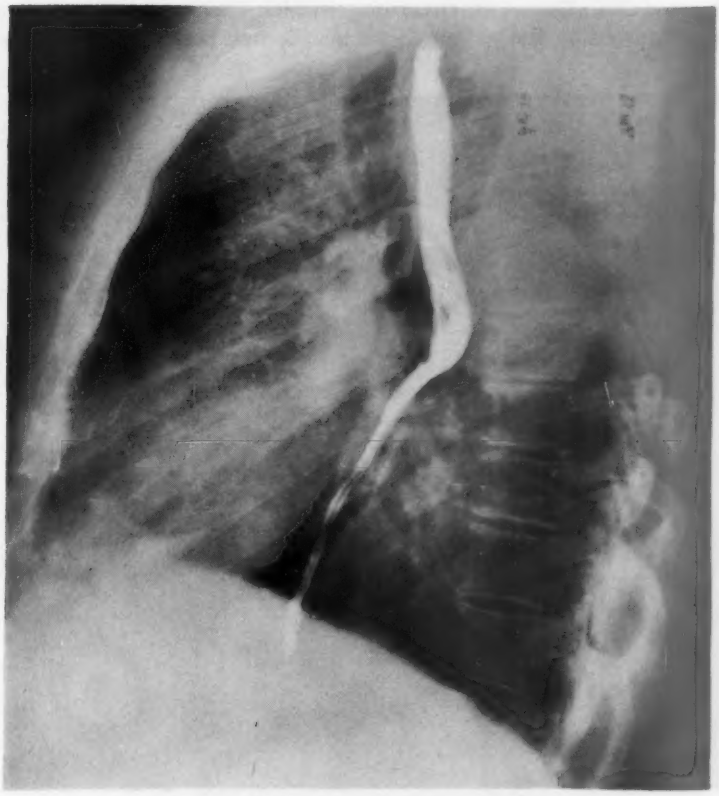


FIG. 4B. Lateral esophagram shows the posterior midthoracic location of the rounded mass. There is forward displacement of the lower esophagus.

The ascending and transverse portions of the thoracic aorta (figure 6C) were slightly dilated (diameter, 42 mm.) but smooth in outline. Abdominal films disclosed multiple sclerotic plaques in the abdominal aorta and iliac arteries.

DISCUSSION

Pathologic Features: Due to the decreasing incidence of tertiary syphilis and increased life expectancy, aneurysms of the thoracic aorta are now more commonly due to arteriosclerosis than to syphilis.[1, 5] The pathologic mech-

anisms responsible for the formation of the arteriosclerotic aneurysm are not entirely clear. De Takats and Pirani [7] believe that the following local factors are of prime importance in the formation of arteriosclerotic aneurysms: deposition of fibrin and hematogenous substances in the intima; accumulation of ground substances and disruption of elastic lamellae in the media, and disturbance of circulation in the vasa vasorum. Atheroma formation, probably due to faulty lipid metabolism, may further weaken the

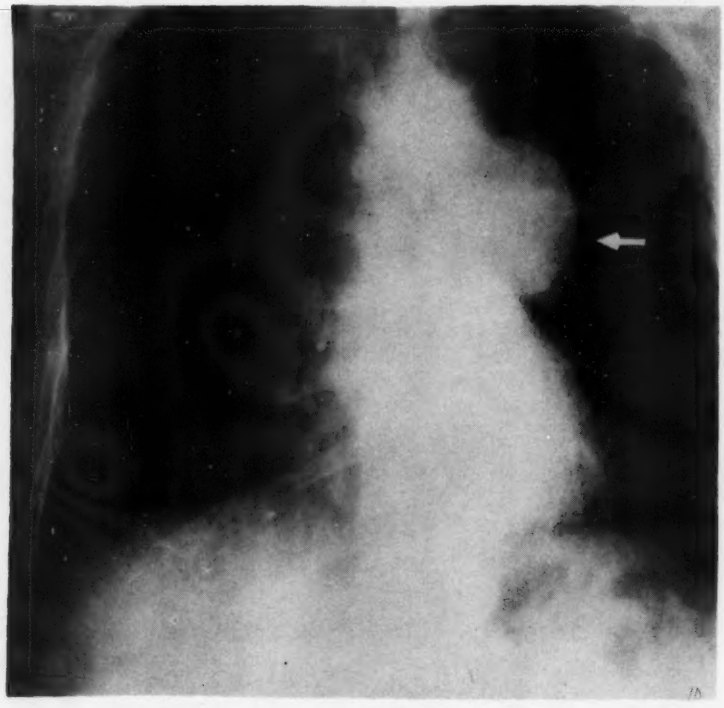


FIG. 4C. Frontal angiocardiogram reveals the opacified aneurysm surrounded by a wall of thrombus (arrow).

arterial wall, form atheromatous ulcers and also cause dilatation. Indeed, mural thrombus formation and fibrosis of the arterial wall and periarterial tissues are attempts to stay the progress of dilatation. The aneurysmal tendency also depends upon the level of systolic pressure, direction and force of secondary blood currents (governed by the physical laws of flow of liquids through tubes), and the state of the vascularization of the aneurysmal wall. It is the latter factor which appears to be the most important and yet least understood, although there is general agreement that the walls of

aneurysms are poorly vascularized. As a result, the fibrous tissue replacing the elastic and muscle fibers are defective and inadequate, and even mural thrombi are only partially organized.

Arteriosclerosis of the thoracic aorta tends to occur in the arch and descending portions of the aorta (figure 7A).[5] This is in contrast to syphilis, where the ascending aorta and arch are usually involved. This is explained by spirochetal localization in the aortic root and ascending aorta

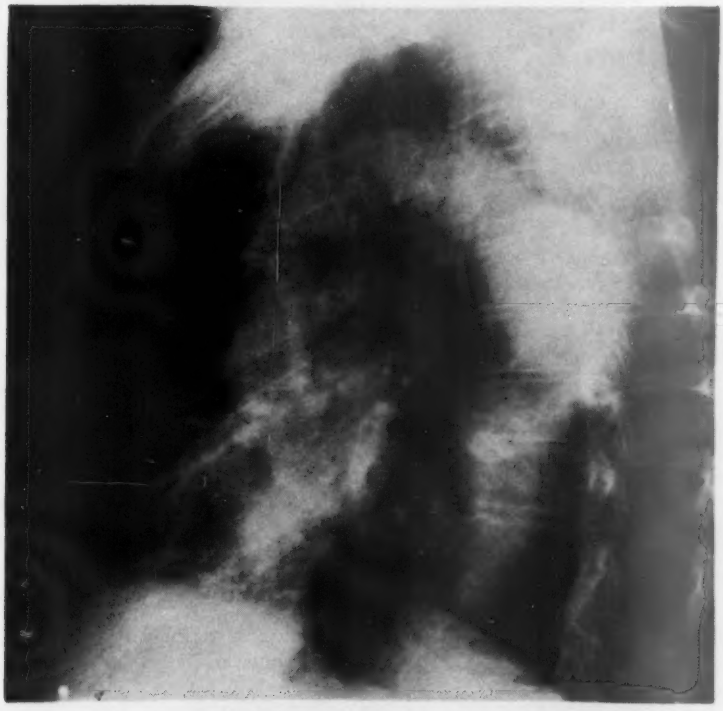


FIG. 4D. Left oblique angiocardiogram demonstrates a normal ascending and transverse thoracic aorta. A large, fusiform aneurysm of the mid-descending aorta is present. Below there is dilatation of the remaining aorta.

because of the abundance of vasa vasorum in those regions. Syphilis causes destruction of all elements of the arterial wall, destruction of elastic and muscle fibers of the media, and severe vasa vasorum endarteritic lesions producing anoxia of the wall and aneurysmal dilatation. In addition, involvement of the aortic valves by the syphilitic process and the development of aortic regurgitation cause increased cardiac output and often hypertension. These stresses favor development of aneurysms of the ascending and transverse portions of the aorta.



FIG. 4E. Photograph of the aneurysm at operation (courtesy of Dr. M. E. DeBakey).

Clinical Features: Incidence: The incidence of arteriosclerotic thoracic aorta aneurysms is difficult to estimate because clinical differentiation from the syphilitic is not always possible. Formerly, most of the aneurysms of the thoracic aorta were believed to be due to syphilis.[4, 5] Now, there is general agreement that arteriosclerotic aneurysms are increasing in incidence.

The present series of six arteriosclerotic aortic aneurysms was collected within a one year period.

Age and Sex: The ages of the six patients when the diagnosis of arteriosclerotic aneurysm of the thoracic aorta was first made varied from 51 to 77 years (mean, 63 years). This is in accord with the average age of death of patients with thoracic arteriosclerotic aneurysms reported by Cranley et al.,[5] and compares favorably with the statistics of Estes [8] and Crane,[9] who found that 66% of the abdominal arteriosclerotic aortic aneurysm deaths occurred



FIG. 5. *Case 5.* Multiple arteriosclerotic aneurysms of transverse and descending thoracic aorta. A. Conventional frontal x-ray shows huge masses, left superior mediastinum, extending into the apex (arrow). Another mass lies adjacent to and is obscured by the left ventricle.

in the sixth and seventh decades. This is in contrast to the average age at death of patients with syphilitic aortic aneurysms, which is in the 40's and 50's.[4, 5, 9] Three of the patients were male and three were female; all were Caucasian.

Symptoms and Physical Findings: Three patients gave a history of long-standing hypertension. In one (case 2), it had been present for 30 years. Backache was the chief complaint in two patients; in case 4 it was severe, sharp and localized in the left scapular area; in case 3 it was accompanied by chest pain. In case 1 the onset was with severe epigastric pain which

radiated into the back and later subsided. Hoarseness was present in one patient (case 1), hemoptysis in another (case 2). One patient was free of complaints referable to the thorax (case 5); weakness and unsteadiness in gait were attributed to advanced age. Only one patient (case 6) had dyspnea, but this was due to advanced pulmonary fibrosis and emphysema.

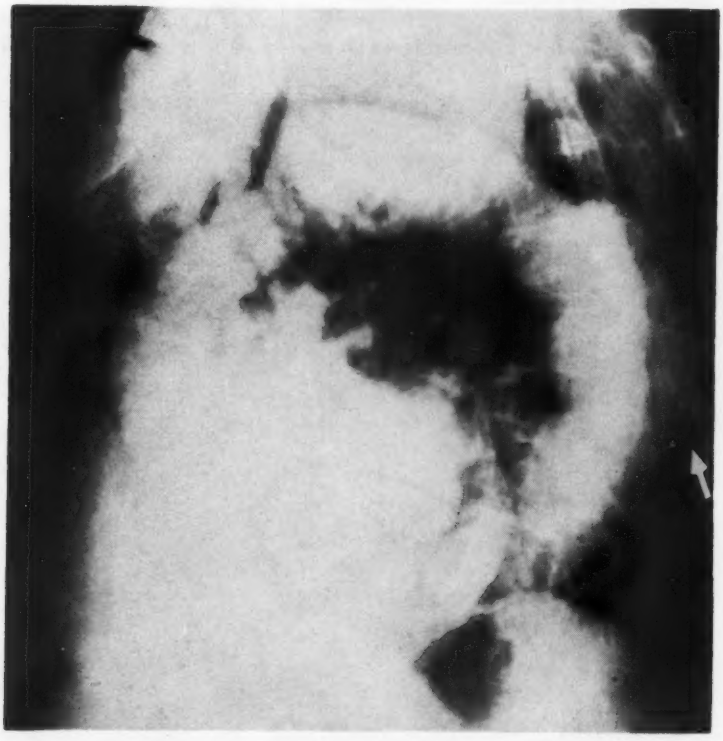


FIG. 5B. Left anterior oblique angiocardiogram reveals the ascending aorta to be of normal size and contour. The transverse portion is aneurysmal and contains thrombus reaching the apex. The descending aorta is tortuous and contains an aneurysm with thrombus along the posterior wall (arrow).

All patients were ambulant and well nourished; none was obese. The blood pressure was elevated in three patients (case 2, 210/170 mm. of Hg; case 4, 220/106 mm. of Hg; case 5, 160/110 mm. of Hg). Tortuous, sclerotic peripheral vessels were found in two (cases 1 and 5). Abdominal aortic masses were not felt, although in case 4 clotting of an unsuspected abdominal aneurysm occurred after homologous grafting of the thoracic aneurysm. In two instances cardiac murmurs were present: in case 2 a presystolic murmur was due to long-standing mitral valvular disease; in

case 5 a high-pitched (grade 4) apical systolic murmur was attributed to mitral valvular sclerosis. One patient (case 1) was found to have paresis of the recurrent laryngeal nerve. Severe pulmonary fibrosis and emphysema were associated diseases in case 6. Serologic tests of the blood for syphilis were negative in all patients.

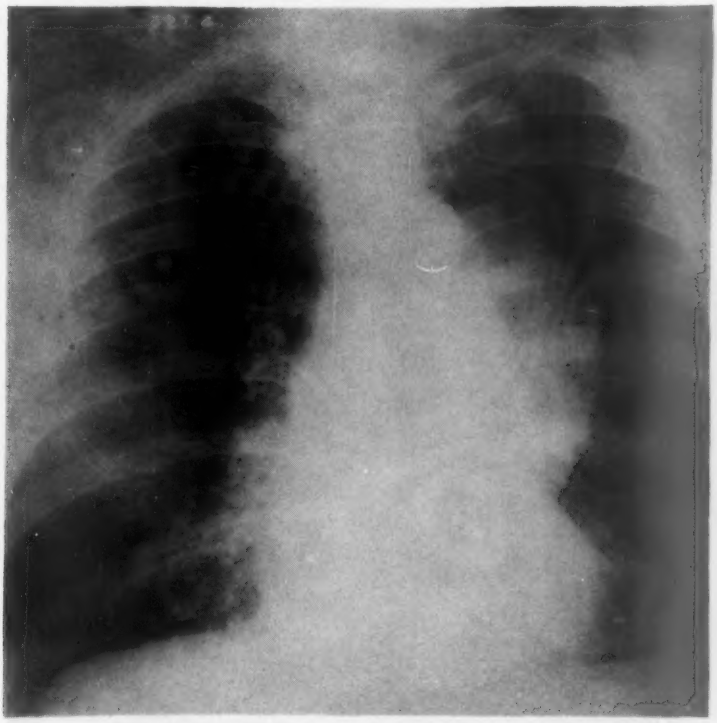


FIG. 6. *Case 6.* Arteriosclerotic fusiform aneurysm descending aorta complicating pulmonary fibrosis and emphysema. A. Conventional frontal roentgenogram shows an enormous left mediastinal and hilar mass. Note the generalized pulmonary fibrosis.

Electrocardiography: Electrocardiographic studies were normal in two patients (cases 1 and 3); showed left axis deviation in three instances, apparently due to hypertension (cases 4, 5 and 6); right bundle branch block in one (case 2); slight prolongation of P-R interval to 0.21 sec. (case 6): and occasional premature beats (case 5). None of the patients had electrocardiographic evidence of coronary artery occlusion or insufficiency.

Roentgenographic Features: Conventional Roentgenography: Conventional roentgenography of the chest provided significant clues for the diagnosis of aortic aneurysms. It disclosed hilar or mediastinal masses and/or

enlarged aortic shadows in every instance. Despite the aortic involvement, pulsatile movements of the aneurysm were usually absent; in fact, pulsation was recognized in only one patient (case 6). Fluoroscopy, however, was valuable for localization of the aneurysms.[10] Study in the left anterior oblique position, which allows a lateral view of the aorta and separates it from the heart, was especially valuable in disclosing aortic unfolding, tor-

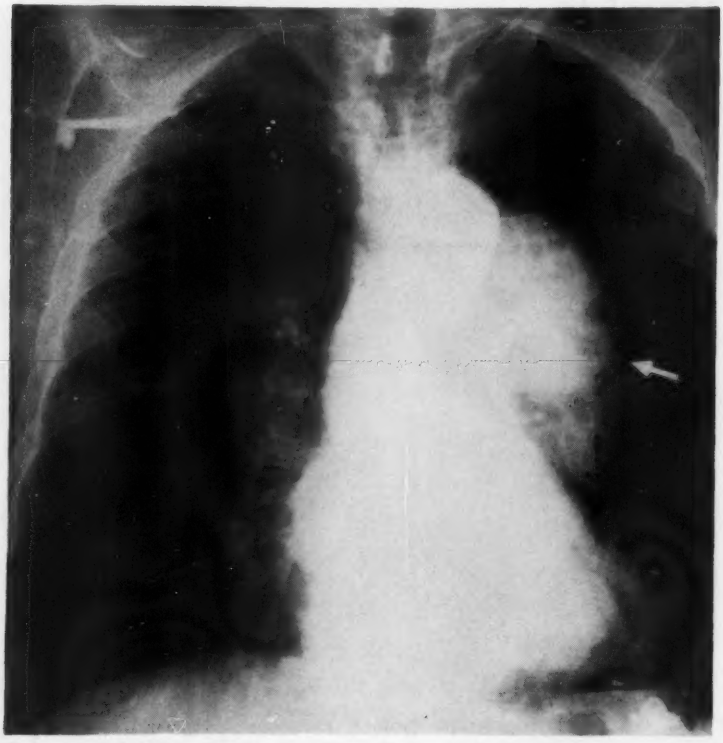


FIG. 6B. Frontal angiocardiogram reveals opacification of the huge, descending aortic aneurysm. Note thrombus along the outer wall (arrow).

tuosity and dilatation. Calcification of the aortic wall and/or aneurysm occurred in two patients: case 2 showed calcification of the aortic knob as well as the aneurysm (figure 2A); case 3 had a rim of calcium lining the transverse aortic aneurysm (figure 3B). Generalized aortic density, a sign of thickening and sclerosis, occurred twice in the descending aorta (figures 1A and B; 3A and B). Esophageal visualization proved valuable for estimating aortic tortuosity (figure 4B).

Special studies (tomography) were necessary to establish the presence

of erosion of vertebral bodies in case 4. Films of the abdomen, especially lateral views, were important for the demonstration of calcium in the abdominal aorta.[11, 13]

Angiocardiography: Angiocardiography, by visualizing the thoracic aorta, provided the definitive diagnosis of aneurysm. In most instances the opacified ascending aorta appeared smooth, regular in outline, and



FIG. 6C. Left anterior oblique angiocardiogram also shows the normal ascending and transverse portions of the aorta; the descending aorta contains a huge aneurysm.

normal or only slightly dilated. In contrast to syphilitic aortitis, the midportion of the ascending aorta was generally less than 38 mm. in diameter (the figure of the upper limit of the normal and arteriosclerotic aorta) (figures 1C, 3D, 4D, 5B).[6, 14-16] Aneurysmal dilatations of the arch and descending portions were clearly demonstrated (figures 1C; 2C and D; 3C and D; 4D; 5B; 6C). Saccular (figures 1C, 2C and D), as well as fusi-

form aneurysms (figures 3C and D; 4C and D; 5B; 6B and C) were differentiated. Furthermore, thrombus within aneurysms explained the absence of pulsations (figures 2C, 3C, 4C, 5B, 6B). Finally, increased aortic wall thickness was especially well delineated (figures 1C and 4D).[17]



FIG. 7. Arteriosclerosis of transverse and descending aorta, 69 year old asymptomatic woman. A. Conventional left anterior oblique x-ray shows pronounced tortuosity, density and medial calcification of the entire transverse and descending thoracic aorta.

It was also possible, in the patient with hemoptysis (case 2), to show left pulmonary artery stenosis by the aortic aneurysm (figure 2B).

Diagnosis: The diagnosis of arteriosclerotic aneurysms of the thoracic aorta may originate with routine roentgen study of the chest, especially in patients over 50 years of age. Roentgen study of the chest is mandatory when there is a history of hypertension, or if hypertension is found and there are complaints of chest pain, backache, hemoptysis, hoarseness or epigastric

pain radiating into the thorax. The presence of mediastinal or hilar masses related to the aorta, especially if pulsatile, should suggest the possibility of aneurysm. However, pulmonary and mediastinal tumors that are intimately related to cardiac chambers or great vessels may also be pulsatile and simulate aneurysms.[6, 18-20] Unfolding, elongation, dilatation and tortuosity of the aorta are common in hypertension and arteriosclerosis,[6, 17] and also need to be differentiated from aneurysms. Enlargement of the aorta due to



FIG. 7B. Left anterior oblique angiocardiogram shows only moderate dilatation of the mid-ascending portion of the aorta. Note the regular and smooth contours of the ascending aorta.

dissecting aneurysm (dissection and hematoma) (figure 8) must also be considered. Aortic anomalies, especially of the arch, may also simulate aneurysms.[6] For these reasons, and because exact delineation of the aneurysm will aid in planning the operative attack and selection of the proper size of the graft, angiocardiography is advocated.

Unlike abdominal aortic aneurysms, which are generally due to arteriosclerosis, the etiology of thoracic aorta aneurysms is difficult to determine, especially if the serologic test and history for syphilis are negative. The lo-

cation of aortic aneurysms is of some importance. Aneurysms of the ascending aorta and transverse aorta in the younger age groups are usually syphilitic; however, aortic dilatation may occur in hypertension and rheumatic aortitis.[14, 15]

The arteriosclerotic process usually involves the transverse and descending aorta and spares the ascending portion (figure 7A). The finding of a



FIG. 8. Left anterior oblique angiocardiogram of a dissecting aortic aneurysm in a 49 year old woman. Note the huge thrombus (arrow) which begins just beyond the left subclavian artery and extends to the base. The descending aorta is markedly compressed.

smooth, undilated and regular ascending aorta on angiocardiography does not rule out syphilis unequivocally. However, such findings are uncommon in syphilitic aortitis.[15, 26]

Other causes of aortic aneurysms should be differentiated from the syphilitic and arteriosclerotic. These are congenital, dissecting and traumatic. Congenital aortic aneurysms are rare and usually occur in the young.[6, 21] Many conditions may cause aortic dissection.[22] A chronic dissecting aneurysm of the aorta may produce a markedly large vessel and, on angiocardi-

ography, be recognized by the widespread narrowing of the aortic lumen (figure 8).[6] Congenital anomalies (kinking) of the aortic arch may simulate a mediastinal tumor and are easily differentiated from aneurysms by angiocardiography.[6, 23-25] Traumatic saccular aneurysms of the arch and descending aorta may have roentgen findings similar to the arteriosclerotic, particularly if they are of long duration and contain calcification.[27] However, a history of trauma of the thorax should make differentiation possible.

Treatment: Hitherto, the treatment of thoracic aneurysms of the aorta was generally ineffectual. Occasionally, excision and suture of an aortic saccular aneurysm are successful.[2, 28] Excision of thoracic aortic aneurysms and replacement by a homograft have become generally accepted as the treatment of choice.[3, 27, 29] Only one patient in our series had an operation (case 4). Unfortunately, an unsuspected abdominal aortic aneurysm became clotted and necessitated simultaneous excision and replacement by a homograft. Had the abdominal aneurysm been detected it would have been excised first, and afterwards the thoracic aneurysm would have been repaired —a course which may have prevented thrombosis of the abdominal aorta aneurysm.[30]

Prognosis: Too few arteriosclerotic aneurysms of the thoracic aorta diagnosed during life are available to estimate the prognosis accurately. In a series of six cases collected during the last year, three are dead: one died suddenly, presumably of aortic rupture (case 1); another died soon after diagnosis, following nailing of a fractured femur (case 3); and the third died following excision and homografting of thoracic and abdominal aortic aneurysms (case 4). Of the three living patients, one (case 5) is asymptomatic despite the presence of two large fusiform aneurysms (operation was not advised by the referring physician); another (case 2) had subsidence of hemoptysis following treatment with hypotensive drugs; and the last patient (case 6) has had marked increase in size of a huge, diffuse aneurysm of the descending aorta over a one year period of observation. (Advanced pulmonary fibrosis and emphysema precluded surgery.)

Summary

Arteriosclerotic aneurysms occur in degenerative disease of the thoracic aorta and are a malady of the elderly. Arteriosclerotic aortic aneurysms may be asymptomatic, but often there is a history of hypertension. When symptoms occur the situation is ominous. Backache may be due to erosion of the bodies of the dorsal vertebrae by the aneurysm; hoarseness can be caused by recurrent laryngeal nerve paralysis; and hemoptysis can be caused by erosion or stenosis of a large pulmonary artery. In a small series of six cases diagnosed with the aid of angiocardiography and herein reported, the majority had symptoms due to the aneurysm; of these, three (50%) were dead within a year.

Diagnosis of aneurysms of the thoracic aorta depends upon the roentgen findings of mediastinal or hilar masses or an enlarged aorta. Differentiation from mediastinal tumors may be difficult, if not impossible. It then becomes necessary to perform contrast studies of the cardiovascular system. Angiocardiography can be depended upon to reveal saccular and fusiform aneurysms, as well as dilatation, tortuosity, unfolding and congenital anomalies of the aorta. The diagnosis of arteriosclerotic aneurysms of the aorta depends upon the presence of a negative history and serologic test for syphilis in the older age groups, and the location of the aneurysm in the arch and descending portions. The absence of severe dilatation and a regular smooth ascending aorta are additional factors that favor the diagnosis of arteriosclerosis. Since the treatment for syphilitic and arteriosclerotic thoracic aneurysms is the same, the etiologic differentiation is often of only academic interest.

The decision to perform surgery for arteriosclerotic thoracic aneurysms must take into account the advanced age and the tendency for arteriosclerosis to occur elsewhere. In the heart, there may be coronary thrombosis or insufficiency; in the brain, cerebral thrombosis or hemiplegia; in the abdomen, aortic aneurysm or occlusion; and in the legs, arterial occlusion or insufficiency. Associated diseases like pulmonary fibrosis and emphysema, and kidney or liver disease, also increase the hazards of the surgical treatment. Despite all these, constant vigilance to detect the case suitable for surgery is recommended. Even though not enough time has elapsed to assess the results properly, excision of the aneurysm and replacement by a graft promise to be effective in prolonging life.

Summario in Interlingua

In recente annos un numero crescente de aneurysmas del aorta thoracic esseva causate per arteriosclerosis. Isto se explica per le facto que le incidentia de syphilis cardiovascular decresce durante que le longevitate accresce. In le passato, le discoperta de aneurysmas aortic esseva de interesse plus tosto academic, proque le application de filos de metallo o de coperturas de cellophan esseva technicas restauratori a successo restringite. Plus recente methodos chirurgic—specialmente le excision del aneurysma e su reimplaciamento per homologe graffos aortic—promitte resultatos de plus alte grados de efficacia therapeutic.

Le precoce diagnose de aneurysma del aorta thoracic es importante. Il pare que le superviventia probabile non es extense si tosto que symptomas como raucitate, hemoptysis, e dorsalgia in consequentia de erosion spinal comencia manifestar se. Le roentgenographia provide felicemente un indicio significative in le forma de anormal umbras mediastinal o hilar. Si le natura vascular del lesion es obscur, visualisation a contrasto effectuate in le aorta thoracic per medio del methodos angiocardiographic va servir a establir le diagnose promptemente.

Es reportate sex casos de arteriosclerotic aneurysma thoracic, con illustrationes roentgeno- e angiocardiographic. On pote fider se al capacitate del angiocardiographia de revelar aneurysmas saccular e fusiforme e de differentiar dilatation, tortuositate, displication, e anormalitates congenite in le aorta. Le diagnose de aneurysma arteriosclerotic del aorta depende del presentia de un negative historia e un negative test

serologic pro syphilis in le caso de patientes del gruppos de etates plus avantiate e del location del aneurysma in le arco e le portiones descendente del aorta. Le absentia de sever dilatation e un regular e lisie portion ascendente del aorta es factores additional que parla in favor del diagnose de arteriosclerosis. Proque le tractamento de syphilitic e de arteriosclerotic aneurysmas thoracic es identic, le differentiation etiologic es frequentemente de interesse exclusivemente academic.

In decider se a interprender un operation chirurgic pro arteriosclerotic aneurysma thoracic, on debe prender in consideration le etate avantiate del patiente e le tendentia del arteriosclerose de manifestar se alterubi. In le corde il pote haber thrombosis coronari o insufficientia coronari; in le cerebro, thrombosis cerebral o hemiplegia; in le abdomine, aneurysmas aortic o occlusion; e in le gambas, occlusion o insufficientia arterial. Morbos associate—per exemplo fibrosis e emphysema pulmonar e disordines renal o hepatic—etiam augmenta le hasardos del intervention chirurgic. In despecto de omne iste limitationes, un vigilantia ininterrumpite debe esser recommendate a fin que le casos que pote profitar del chirurgia es promptemente detegite. Le excision del aneurysma e le substitution de un graffo promitte provar se un mesura effiçace in prolongar le vita del patiente, ben que il es ver que le tempore que ha passate depost le introduction de iste methodo es non ancora satis extense pro evalutar le resultatos definitivemente.

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DIFFERENTIAL DIAGNOSIS OF THE PAIN OF CORONARY HEART DISEASE*

By A. Carlton Ernstene, M.D., F.A.C.P., *Cleveland, Ohio*

The three most common clinical manifestations of coronary heart disease are, in their order of frequency, angina pectoris, acute myocardial infarction and acute coronary failure. Each of these conditions is characterized by pain in the chest due to anoxia of one or more areas of the myocardium. The pain is similar in location in all three, and the syndromes are distinguished from one another chiefly by the length of time the distress persists and by whether the anoxia is of sufficient severity and duration to result in the death of myocardial tissue. Pain in the chest may also be caused by many other conditions. In most of these the clinical history clearly indicates a noncardiac source. In some, however, the discomfort strongly suggests myocardial ischemia, and diagnostic errors can be avoided only by detailed analysis of the symptoms and thorough examination, including electrocardiographic and roentgenologic study.

Angina Pectoris: Attacks of angina pectoris may be induced by exertion, emotion, a large meal, sudden exposure to cold, or a disproportionate reduction in coronary blood flow during sleep. The pain typically originates in the retrosternal area, most commonly in the middle or upper third, and may or may not radiate to one or both upper extremities, the neck, jaws, roof of the mouth, mid-dorsal or left scapular region, or the epigastrium. When induced by exertion, the distress usually is mild at the very beginning and then rapidly becomes so severe that the patient is quickly forced to cease all activity. Rest as a rule gives relief within a few minutes, and nitroglycerin almost always shortens the duration of symptoms still further. Many persons describe their discomfort not as actual pain, but rather as a sense of constriction, tightness, gas, choking, burning, pressure, aching, heaviness or fullness. There may be an accompanying desire to belch. In these instances the patient often attributes his symptoms to indigestion rather than to exertion, and may be of the opinion that relief depends more on getting rid of a small amount of gas than on rest.

Instead of arising in the substernal area, the pain of angina pectoris may first be felt in any one of a number of less typical locations, such as the precordium, lower left axilla, right or left infraclavicular region, mid-dorsal or left scapular area, various parts of one or both upper extremities, the

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From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Requests for reprints should be addressed to A. Carlton Ernstene, M.D., The Cleveland Clinic, 2020 East Ninety-third Street, Cleveland 6, Ohio.

throat, jaws or epigastrium. There is often prompt radiation from these less common sites of origin to the substernal region, and knowledge of this is of help in diagnosis. If such radiation does not occur the distress may be wrongly interpreted, unless careful inquiry is made concerning the relationship to exertion, emotion or meals, and the relief afforded by rest. A therapeutic trial with nitroglycerin may help to clarify the diagnosis.

About one-half of all patients who have angina pectoris have a normal electrocardiogram. When no electrocardiographic abnormalities are present, and doubt exists as to the diagnosis, the two-step exercise test or the anoxemia test may give helpful information. A positive result can be expected, however, in not more than 60% of all cases in which the control record is normal.

There are several conditions which may cause pain similar to that of angina pectoris. Among these are esophageal hiatus hernia, cardiospasm and spasm of the esophagus, and osteoarthritis of the upper dorsal spine. Pain due to any of these conditions may be situated in the retrosternal area, but almost always can be differentiated from the pain of angina pectoris on the basis of differences in the precipitating factors, duration, and the measures which give relief.

The pain of cardiospasm or esophagospasm is not related to physical exertion, but may be induced by excitement or by rapid eating or drinking. The discomfort usually lasts longer than that of angina pectoris. Nitroglycerin may give prompt relief, but a few sips of hot water often are equally helpful. Pain resulting from esophageal hiatus hernia is seldom precipitated by exertion, but may be brought on by a large meal or by bending sharply forward, as in tying one's shoestrings. In addition, it often occurs while the patient is recumbent. A moderate or severe anemia is present at times, due to loss of blood from the congested mucosa of the herniated portion of the stomach or from a peptic ulcer in that area. This is an important feature because, in patients who have asymptomatic coronary atherosclerosis, the development of anemia from any cause may result in the appearance of typical attacks of angina pectoris. An esophageal hiatus hernia may therefore be the indirect cause of angina, and correction of the anemia may restore the exercise capacity to normal. It must be remembered, also, that many patients who have an esophageal hiatus hernia are of the age group in which coronary heart disease is common. An occasional person will be encountered who is experiencing both angina pectoris and symptoms due to hiatus hernia. Surgical repair of the hernia will not reduce the frequency or severity of the attacks of angina pectoris. Therefore, in patients who have a hernia of this type, symptoms suggestive of coronary heart disease should be evaluated carefully in order to avoid the error of giving unwarranted assurance concerning the benefit to be expected from surgery.

Osteoarthritis of the dorsal spine occasionally causes pain in the anterior chest, with little or no accompanying discomfort in the back. In contrast

to angina pectoris, the pain is usually sharp or aching in quality and is induced by use of the arms, raising the shoulders, twisting or bending, or turning over in bed. Walking may fail to cause symptoms, and nitroglycerin does not give relief.

The number of cases of angina pectoris which are not correctly recognized is far exceeded by the number in which symptoms not related to the heart are wrongly attributed to coronary insufficiency. Although the conditions just mentioned are responsible for occasional errors of this kind, a far more frequent cause is incorrect interpretation of the sticking or aching precordial pain encountered so frequently in neurocirculatory asthenia and states of anxiety, fatigue or nervous tension. The pain in these conditions is not retrosternal in location and does not radiate to that area. At times, however, it spreads upward toward the left shoulder and even down the left arm, usually along the lateral aspect. The sharp or sticking variety of pain may be of no more than momentary duration, but the dull or aching type and that which is described as a sense of heaviness frequently last for hours at a time. The discomfort is not induced by physical activity but may develop after a period of exertion. Rest and nitroglycerin fail to give prompt relief. Misinterpretation of the complaint undoubtedly is the most common cause of iatrogenic heart disease, and the principal reason for error is failure to appreciate the difference in significance between precordial and retrosternal pain. The pain of angina pectoris is occasionally precordial in origin, but in such cases there almost always is an immediate spread to the retrosternal area.

Acute Myocardial Infarction: The pain of acute myocardial infarction is similar in location and radiation to that of angina pectoris but, with exceptions, is of greater severity. It usually lasts for more than one-half hour and often for several hours, depending on the size of the infarct, the patient's tolerance to pain, the state of the sensorium, and the promptness with which treatment is started. Nitroglycerin is without effect, and morphine gives only gradual relief. Symptoms of shock of mild to severe degree frequently appear soon after the onset. These features readily distinguish myocardial infarction from angina pectoris but do not differentiate it from the syndrome of acute coronary failure. Confirmation of a clinical diagnosis of acute infarction rests entirely on the development of evidence of acute necrosis of myocardial tissue. Fever, leukocytosis, elevation of the erythrocyte sedimentation rate, a rise in serum glutamic oxalacetic transaminase activity, a pericardial friction rub, and characteristic changes in the electrocardiogram are the chief manifestations of this process, and one or more of them must appear subsequent to the onset of symptoms before the diagnosis can be considered established. Fever and leukocytosis usually develop within 24 to 48 hours after the onset of pain, and the erythrocyte sedimentation rate becomes accelerated within the first three or four days. A two- to tenfold rise in serum glutamic oxalacetic transaminase occurs within the first 24

hours and persists for from three to seven days.[1] A pericardial friction rub is detected in approximately 10% of all cases, and may last for a few days or for only a few hours. The electrocardiogram shows diagnostic changes in practically every patient if records are made at daily intervals and if multiple precordial leads are used in addition to the standard and unipolar limb leads. Occasionally a high lateral or a small posterior infarct produces no more than nonspecific changes in the conventional leads, and an electrocardiographic diagnosis requires further exploration over the left upper chest, left axilla and left side of the back.

In the literature on myocardial infarction, attention has been directed repeatedly to the fact that the pain may simulate or be simulated by that of biliary colic or acute surgical conditions in the upper abdomen. Actually, there are very few cases in which the resemblance is so close that a real danger of erroneous diagnosis exists after a careful history and physical examination. When the pain of acute infarction originates in the upper abdomen, there almost always is prompt radiation to the retrosternal area, or at least accompanying distress in that region. This feature, or the presence of such cardiac abnormalities as gallop rhythm and heart sounds of poor quality, should lead to thorough electrocardiographic study.

There are a few conditions which may present a more difficult problem in differential diagnosis. The most important of these are acute nonspecific pericarditis, pulmonary embolism and other conditions which cause a sudden or severe increase in pressure in the pulmonary artery, and dissecting aneurysm of the aorta.

The pain in acute idiopathic pericarditis is usually substernal in location but is not accompanied by symptoms of shock. It is increased by deep breathing but not by walking. A pericardial friction rub is present from the beginning of the illness, in contrast to its appearance after an interval of days in myocardial infarction. In acute pericarditis, also, fever, leukocytosis and elevation of the sedimentation rate are present at the onset and may even antedate the pain. In many cases there is a history of a preceding infection in the upper respiratory tract. The electrocardiogram commonly shows changes which may or may not be diagnostic of pericarditis but are, as a rule, readily distinguishable from those of acute infarction.

Embolic occlusion of the pulmonary artery or one of its major branches may result in sudden death or cause the abrupt onset of severe dyspnea accompanied by cyanosis, retrosternal pain or oppression, and the rapid development of a state of shock. If the condition is not promptly fatal, fever and leukocytosis usually appear within 24 hours. The clinical picture is thus similar to that of myocardial infarction, but massive pulmonary embolism also is attended by the development of a number of signs which are of value in differential diagnosis. The sudden increase in pressure in the pulmonary artery frequently results in accentuation of the pulmonary second sound and a palpable or visible pulsation in the left second intercostal

space adjacent to the sternum. Gallop rhythm may be present over the pulmonary area, and at times a friction rub is heard in this region due to irritation of the pericardium by the dilated pulmonary artery. Right ventricular dilatation and failure often follow, and the peripheral venous pressure then becomes elevated. The electrocardiogram frequently shows temporary changes consisting of a deep S_1, prominent Q waves and inverted T waves in Lead III, and inversion of the T waves in Leads V_2 and V_3. In other instances, there is transient right bundle branch block.

Substernal pain or oppression similar to that produced by pulmonary embolism may result from several other conditions which cause pulmonary hypertension. Among the most common of these, as pointed out by Viar and Harrison [2] in a recent review, are mitral valve disease, emphysema of the lungs, bronchial asthma, and certain forms of congenital heart disease. Severe left ventricular failure is a rare cause. Most patients who have pulmonary hypertension do not experience pain, and it appears that in order for pain to occur the increase in pulmonary artery pressure must not only be of considerable degree but must also develop rapidly or be subject to abrupt exacerbations. In patients who have bronchial asthma, for instance, the pain may occur only during asthmatic attacks. The distress itself probably is due to distention of the pulmonary artery.

Pulmonary hypertension pain may last for a few minutes or for several hours. It may come on only with exertion, and be relieved promptly by rest, and in such instances it can readily be confused with angina pectoris. More prolonged pain may be wrongly interpreted as due to acute myocardial infarction, especially if the electrocardiogram by chance shows changes indicative of myocardial damage. There are several features, however, which are of value in distinguishing the pain of pulmonary hypertension from that of coronary heart disease. In the first place, the presence of a condition capable of causing pulmonary hypertension should warn against making a diagnosis of coronary heart disease until after careful study eliminates the possibility of pulmonary hypertension pain. The distress of pulmonary hypertension is seldom relieved by nitroglycerin and is accompanied by more severe dyspnea than is usual in angina pectoris and acute myocardial infarction. Patients who have pulmonary hypertension generally have a history of chronic cough, and either persistent or intermittent cyanosis is common. Electrocardiograms and roentgenograms of the thorax often reveal evidence of right ventricular hypertrophy, which is rarely present in patients who have coronary artery disease. Finally, oxygen usually gives more striking relief from the distress of pulmonary hypertension than from pain of cardiac origin.

Although dissecting aneurysm of the aorta in its fully developed stage does not present a difficult problem in diagnosis, the early symptoms may be highly suggestive of acute myocardial infarction. The pain often originates in the anterior chest but is abrupt in onset, in contrast to its more

gradual evolution in acute infarction. It lasts for 48 hours or longer, and often persists in greater or less degree until death occurs. Repeated injections of morphine afford only partial and temporary relief. The pain may radiate to the back, arms, abdomen or legs, and there may be symptoms and signs of impairment of the arterial circulation to the brain or one or more extremities. Injury to the nutrient arteries of the spinal cord may result in paresthesia or paralysis of the legs. Hypertension is usually present and is often maintained throughout the illness. The intensity of the heart sounds is not diminished, and, except in rare instances where coronary blood flow is interfered with by proximal dissection of the aneurysm, the electrocardiogram does not show the changes of myocardial infarction.

Two other conditions whose initial symptoms may at times suggest acute myocardial infarction are spontaneous mediastinal emphysema and spontaneous rupture of the esophagus. Spontaneous mediastinal emphysema occurs in previously healthy young adults and is characterized by the sudden onset of pain in the substernal region, which may radiate to the neck, shoulders or arms. There is no shock, and the electrocardiogram does not show the changes of myocardial anoxia or infarction. The pathognomonic feature of the condition, however, is the presence of a to-and-fro crunching or crackling sound (Hamman's sign) over the sternum and precordium synchronous with the heart beat and at times audible only with the patient in certain positions. Roentgenograms of the thorax may reveal shadows of air in the mediastinum.

Spontaneous rupture of the esophagus causes agonizing substernal pain which, in the past, has often been attributed to acute myocardial infarction. There are a number of features which should enable one to avoid an error of this kind. Spontaneous esophageal rupture is a result of severe vomiting and should be suspected whenever intense and persistent retrosternal pain develops after emesis. Subcutaneous emphysema may appear in the neck, and roentgenograms of the thorax may demonstrate mediastinal emphysema and the escape of orally administered iodized oil into the mediastinum. Treatment, of course, consists of prompt surgical repair.

Acute Coronary Failure: In 1940, Blumgart and his associates [3] focused attention on a previously neglected form of coronary heart disease characterized by attacks of substernal pain of longer duration than in angina pectoris but not followed by clinical or electrocardiographic evidence of myocardial infarction. The physiologic basis for the pain in this condition is the same as in angina pectoris, namely, a reversible myocardial anoxia. The anoxia lasts longer than in angina pectoris but not long enough to cause myocardial necrosis. The pain persists for 20 minutes or longer, may be of any intensity from mild to severe, and at times is accompanied by some respiratory distress, sweating and weakness. Nitroglycerin fails to give more than partial and temporary relief. Fever, leukocytosis and an elevated

sedimentation rate do not occur, and there is no significant increase in serum glutamic oxalacetic transaminase activity. Electrocardiograms made during the attack may show changes similar to those which occur in many patients during seizures of angina pectoris. The changes, when present, are of short duration, and subsequent tracings fail to show the serial alterations of acute infarction. Acute coronary failure must be distinguished not only from angina pectoris and acute myocardial infarction but also from the various disturbances which may simulate either of these conditions. Recognition of the syndrome is important because, among other considerations, the attacks at times represent the premonitory symptoms of impending infarction.

The Anterior Chest Wall Syndrome: Prinzmetal and Massumi [4] recently described a syndrome characterized by persistent, continuous pain in the anterior chest wall, often with periodic exacerbations which suggest angina pectoris or repeated episodes of acute coronary failure. Although the syndrome may occur in the entire absence of organic heart disease, many of the patients have had earlier myocardial infarction, and in these the pain first develops a few weeks to a few months after the onset of the attack. It is in such instances especially that there is danger of erroneous interpretation of the complaint. The mechanism of the disturbance is not known, but in the post-infarction type an analogy to the shoulder-hand syndrome has been suggested. The pain often persists for weeks or months, and may involve the entire anterior chest wall, but usually is most severe in the sternal or precordial region. The paroxysmal increases in severity last from a few minutes to several hours. They are not brought on by walking but may be induced by quick movements of the body or by use of the arms. Nitroglycerin does not give relief. Electrocardiograms taken during these attacks show no change from records made in the intervals between them. On physical examination there is striking tenderness of the chest wall. According to Prinzmetal and Massumi, breathing exercises, corticotropin, cortisone and x-ray therapy usually give prompt relief from all discomfort. In the post-infarction type of the syndrome, the patient often interprets the pain as indicative of further damage to the heart. It is important, therefore, that the physician be aware of the condition so that he may reassure the patient promptly and avoid needless restrictions on activities and the possible development of an anxiety neurosis.

Summary

In most of the noncardiac conditions which cause pain in the chest, the clinical history clearly indicates the source of the symptoms. However, the precordial discomfort of neurocirculatory asthenia and anxiety states often is interpreted erroneously, and there are several conditions which produce pain highly suggestive of coronary heart disease. Esophageal hiatus hernia, cardiospasm or spasm of the esophagus, and osteoarthritis of

the upper dorsal spine may cause distress similar in location to that of angina pectoris. The pain of these conditions usually can be differentiated from that of angina pectoris on the basis of differences in precipitating factors, duration, and the measures which give relief. In the anterior chest wall syndrome, periodic exacerbations of pain are common and may be wrongly attributed to angina pectoris or to repeated episodes of acute coronary failure. Distinguishing features include a lack of relationship to walking, failure to respond to nitroglycerin, and the absence of electrocardiographic changes during the paroxysms. The pain of massive pulmonary embolism, acute idiopathic pericarditis, dissecting aneurysm of the aorta, spontaneous mediastinal emphysema, and spontaneous rupture of the esophagus may closely simulate that of acute myocardial infarction. Errors in diagnosis can be avoided by detailed analysis of the symptoms and thorough examination, including electrocardiographic and roentgenologic study.

SUMMARIO IN INTERLINGUA

In le majoritate del conditiones noncardiac que causa dolores thoracic, le historia clinic indica clarmente le origine del symptomas. Tamen, le discomforto de asthenia neurocirculatori e de statos de anxietate evoca frequentemente interpretationes erronee, e il existe plure conditiones que causa dolores facilemente interpretabile como indicios del presentia de morbo cardiac coronari. Hernia del hiato esophagee, cardiospasmo o spasmo del esophago, e osteoarthritis del spina dorsal superior pote producer gravamines de location simile a illos de angina de pectore. Le dolor de iste conditiones es usualmente differentiabile ab le dolor de angina de pectore super le base de differentias in le factores precipitatori, in duration, e in le messuras que effectua alleviation. In le syndrome del pariete antero-thoracic, exacerbationes periodic de dolor es satis commun e pote esser attribuite erroneemente a angina de pectore o a repetite episodios de acute disfallimento coronari. Lor characteristicas differentiatori include occurrentia independente de ambulation, nonresponsa a nitroglycerina, e absentia de alterationes electrocardiographic durante le paroxymos. Le dolores de massive embolismo pulmonar, acute pericarditis idiopathic, aneurysma dissecante del aorta, spontanee emphysema mediastinal, e spontanee ruptura del esophago pote simular le dolores de acute infarcimento myocardial con alte grados de verosimilitude. Errores diagnostic pote esser evitate per le analyse detaliate del symptomas e per examines meticulose, incluse studios electrocardiographic e roentgenologic.

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THE SIGNIFICANCE OF NONBACTERIAL THROMBOTIC ENDOCARDITIS: AN AUTOPSY AND CLINICAL STUDY OF 78 CASES *

By Richard A. MacDonald, M.D., and Stanley L. Robbins, M.D.,
Boston, Massachusetts

The purpose of this paper is to call attention to the relatively unappreciated fact that nonbacterial thrombotic endocarditis has a clinical as well as a pathologic significance. Previous workers have studied this type of endocarditis from the standpoint of its histologic features, so that up to the present time there have been no studies correlating clinical and autopsy findings. From a review at the Mallory Institute of Pathology there is evidence that in a certain number of cases emboli may arise from the valvular vegetations and cause premortem infarction of organs. These infarctions in some cases contribute to death, and may in rare instances be the sole cause of death.

The subject of nonbacterial thrombotic endocarditis has been confused by the use of different terms by different writers and by the fact that new terminology has lately been proposed. This multiplicity of terms should be reduced in number. Among the names which have been previously used and which may be discarded because, as will be shown, they do not denote the true nature of the condition are terminal endocarditis, marantic endocarditis, endocarditis simplex, and degenerative verrucal endocardiosis.

Review

Libman [1] differentiated a nonbacterial indeterminate endocarditis from bacterial, rheumatic and syphilitic types. He further subdivided the indeterminate type into atypical verrucous, nonbacterial thrombotic, and an unclassifiable type. He did not report a large number of the nonbacterial thrombotic type, but he outlined a view that has subsequently been repeated, namely, that the lesions had no clinical significance and occurred as a terminal event in patients with wasting diseases. He added in a later article [2] that the vegetations might occasionally give rise to emboli. Gross and Friedberg,[3] after a study of 47 cases, stated that ". . . nonbacterial thrombotic endocarditis is viewed as an accidental occurrence in the course of any fatal disease, without appreciable clinical significance." They found rheumatic valvular damage in 40 of their 47 cases, and stated that the development of the verrucal lesions was probably dependent on previous damage to

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From The Mallory Institute of Pathology, Boston City Hospital, Boston, Massachusetts.
Requests for reprints should be addressed to Richard A. MacDonald, M.D., Mallory Institute of Pathology, Boston City Hospital, Boston 18, Massachusetts.

the cardiac valves. Allen and Sirota,[4] in a histologic study of 50 cases, differed with previous work in regard to the nature of the endocardial lesions. They considered the lesions to be of valvular and not thrombotic origin, consisting primarily of swollen, degenerated collagen of the valves. They expressed the view that the lesions were not necessarily terminal, but occurred during the course of both acute and chronic diseases, and although the lesions could and did at times heal, they presented an important morphologic basis for the development of bacterial endocarditis. As recently as 1953 an excellent textbook on the pathology of the heart [5] stated that nonbacterial thrombotic endocarditis was ". . . obviously without appreciable clinical significance." A different view was expressed in a recent clinical-pathologic discussion of a case [6] in which clinical importance was attributed to the autopsy finding of nonbacterial thrombotic endocarditis.

Material and Methods

1. Seventy-eight cases of nonbacterial thrombotic endocarditis occurring among 18,486 consecutive autopsies at the Mallory Institute of Pathology were studied. Hematoxylin and eosin stains were routinely used for the tissue preparations, with phloxine methylene blue, elastica, and special stains in some instances. Nearly all the cases had complete (unrestricted) autopsies performed, and all had postmortem bacteriologic studies, consisting in most cases of cultures of the heart, spleen, lower lobes of the lungs, and smear and culture of the valvular vegetations. Additional cases were discarded because on examination they proved to be rheumatic or bacterial in type, or because adequate bacteriologic studies had not been done. In 49 of the 78 cases, histologic sections showing the adherence of the vegetations to the valve were available. In 11 additional cases, the vegetations had separated away from the valve and the adherence itself could not be studied. Histologic sections of the affected valve were not available in the 18 remaining cases, but these had been studied at the time of the autopsy, and gross, microscopic and bacteriologic records were reviewed.

2. A comparative microscopic study was made of bacterial, rheumatic and atypical verrucous endocarditis.

3. The clinical records of the 78 patients with nonbacterial thrombotic endocarditis were reviewed.

Observations

1. *General:*

Age and Sex Incidence: Forty of the patients were females, 38 were males. The age distribution is shown in table 1. The youngest patient was 18 years, and the oldest was 90 years of age. Sixty-nine of the 78 patients (88%) were over the age of 49.

Duration of Illness: The range of the duration of illness before death

TABLE 1
Age Distributions of 78 Patients

10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
1	0	5	3	11	18	25	14	1

was one day to two years, with an average of three months and a median of two months. Seventeen of the 78 patients (22%) were ill less than eight days, and 27 (35%) were ill less than 15 days.

Principal Illnesses: The chief illnesses leading to death (which in each case was not necessarily the acute cause of death) are summarized in table 2.

2. Morphology:

Types of Heart Disease at Autopsy: The most common type of underlying heart disease in this series was arteriosclerotic, which occurred 43 times (55%). Next was rheumatic, which in all cases was inactive and healed. This occurred in 14 cases (18%); the hypertensive arteriosclerotic type was found in seven (9%); and the hypertensive type in six instances (8%). In eight cases (10%) no heart disease was demonstrated.

Valves Involved: The mitral valve alone was involved in 43 instances, the aortic valve alone in 15 instances, while the two combined were involved in 14 cases. A combination of the mitral, aortic and tricuspid valves was found three times, aortic and tricuspid once, and pulmonic and tricuspid valves alone in one instance each.

TABLE 2
Principal Illnesses in 78 Cases

Cancer		27
Stomach	8	
Lung	4	
Pancreas	4	
Gall-bladder or ducts	2	
Liver	2	
Rectum	2	
Lymphoma	2	
Leukemia	1	
Cecum	1	
Breast	1	
Heart failure		13
Cerebral vascular accident		11
Pneumonia		7
Acute myocardial infarction		5
Pulmonary embolus		4
Hepatic coma		2
Acute pyelonephritis		2
Advanced pulmonary tuberculosis		2
Acute glomerulonephritis		1
Liver abscess		1
Ulcerative colitis		1
Peritonitis from perforated viscus		1
Vascular infarction of bowel		1
Total		78

Gross Types of Valvular Lesions: The five gross types of valvular vegetations as described by Allen and Sirota, slightly modified, were found to be a convenient classification, and are as follows: A small univerrucous type, consisting of a single nodule less than 3 mm. in diameter; a small multiverrucous type, more than one nodule, each 3 mm. or less in diameter; a large univerrucous type, a single nodule greater than 3 mm. in diameter; a large multiverrucous type, each nodule greater than 3 mm. in diameter; and a healed type, consisting of any of the above types that have organized and healed. This latter requires microscopic examination to diagnose with certainty. Forty-two of the cases in this series were of the small multiverrucous type, 20 of the small univerrucous type, six of the large multiverrucous type, three of the healed type, and two of the large univerrucous type. Five cases could not be classified because of lack of histologic material and lack of appropriate gross descriptions.

Microscopic Examination of Valves and Vegetations: In the 49 cases in which histologic sections could be examined and which showed the adherent thrombus, and in 11 additional sections of valves without adherent thrombus, the involved valves were abnormal in every instance, including cases in which no anatomic heart disease had been present. In all cases the abnormality consisted of focal or diffuse areas within the valve cusp where the valve tissue was swollen, degenerated and fibrocollagenous, and took an eosinophilic stain. From some degenerated areas small extrusions of fibrocollagenous tissue extended into the cardiac chamber, and may have served as a nidus for thrombus formation, for it was at the site of such focal degenerated areas of valve that thrombi composed of fibrin, platelets and blood cells were attached. In five cases the verrucae were composed of fibrocollagenous tissue of the valve cusp only, without adherent blood thrombus at the external surface; two of these were consistent with the degenerative type of verrucae described by Allen and Sirota; three were considered to represent a healed type because of residual cellular reaction.

The important microscopic feature of the affected valve in each case was the relative lack of cellularity of the area overlaid by thrombus; this finding is of value in differential diagnosis and will be discussed later. In cases where the vegetation had been present for some time, as determined by the degree of organization of the vegetations, a minimal cellular reaction was often present in the valve, and consisted of scattered fibroblasts and Anitschkow's myocytes, with only rare macrophages and lymphocytes.

Associated Thrombotic Findings at Autopsy: Twenty-one of the 78 patients (27%) also had thromboses within vessels or in the cardiac chambers. In six cases the leg veins alone were involved. In seven the heart was involved by mural thrombi; in two of these cases there were associated recent myocardial infarctions; in five cases there were no myocardial infarctions. Four of these latter five cases with mural thrombi were of the usual type, being somewhat large, involving the right auricle

in two cases, both auricles in one case, and the left auricle in one case. In the fifth case, the right auricular endocardium at the site of the obliterated foramen ovale contained vegetations identical to those on the adjacent valve leaflet. One case of mural thrombus of the heart was associated with a partial thrombosis of the inferior vena cava.

Other sites of thrombus formation were as follows: There were two instances of mural thrombi of the aorta, occurring in arteriosclerotic aneu-

TABLE 3

Eleven Patients with Infarctions of Organs Ascribed to Emboli Arising from Valvular Vegetations of Nonbacterial Thrombotic Endocarditis

Case	Autopsy	Principal Diagnosis	Heart Disease	Cardiac Rhythm	Sex	Age	Organs Infarcted	Valve Vegetations	Type of Verrucae
(Group One)									
1	42–392	Carcinoma of stomach	ASHD	NSR	F	52	Skin, spleen, brain, kidneys, coronary artery, lung	Aortic Mitral Tricuspid	Large multi
2	44–334	Heart failure	RHD	AF	F	72	Brain, bowel, kidneys	Mitral	Large uni
3	46–86	Heart failure	RHD	AF	F	50	Brain, spleen, kidney	Mitral	Large multi
4	46–450	Cerebral vascular accident	RHD	AF	F	62	Brain, spleen, kidneys, bowel	Aortic Mitral	Small multi
5	47–28	Heart failure	HASHD	NSR	M	54	Brain, spleen, kidney	Aortic	Small multi
(Group Two)									
6	49–788	Carcinoma of pancreas	ASHD	NSR	F	75	Spleen, kidneys, lungs, popliteal artery (?)	Aortic Mitral Tricuspid	Small multi
7	48–183	Heart failure	ASHD	AF	M	73	Kidneys	Aortic	Small multi
8	48–204	Carcinoma of liver	ASHD	NSR	M	74	Brain, adrenal, kidneys, (lungs)	Aortic	Small uni
9	48–646	Carcinoma of stomach	ASHD	NSR	M	64	Brain, spleen, (lungs)	Aortic Mitral	Small multi
10	48–729	Carcinoma of rectum	None	NSR	F	75	Spleen, kidneys, (lungs)	Aortic Mitral	Large multi
11	48–789	Carcinoma of stomach	ASHD	NSR	M	82	Brain, kidneys, spleen, (lungs)	Aortic	Small multi

ASHD: arteriosclerotic heart disease.
RHD: rheumatic heart disease.
HASHD: hypertensive arteriosclerotic heart disease.
NSR: normal sinus rhythm.
AF: auricular fibrillation.
F: female.
M: male.

rysms of the abdominal portion, and two cases in which fibrin thrombi were found in glomeruli, spleen, liver and heart. There was one instance each of thrombosis of the veins of the periprostatic venous plexus, the splenic vein, the renal artery and the pulmonary artery.

For comparison with these figures, the incidence of thromboses in 18,486 autopsies, at the above named sites and including thromboses of the mesenteric and portal veins, was 1,188 or 6.4%. These percentage figures can be compared only in a broad sense, and are not suitable for statistical analysis.

The figures for thromboses in the 18,486 autopsies were obtained from card index files of autopsy diagnoses, while each of the 78 cases was individually reviewed.

Associated Cancer and Heart Failure: Cancer was found in 28 of the 78 cases (36%). In one case it was an early incidental finding and is not listed in table 2. Heart failure as demonstrated at autopsy was the principal condition in 13 patients, and complicated the illness causing death in an additional 10 cases, a total of 23 cases, or 30%.

3. *Clinical and Morphologic Correlation:*

Cases with Emboli Arising from Valvular Vegetations: There were 11 patients in this series of 78 in whom multiple embolic infarctions of organs were found, with the source of the emboli considered to have been the valvular vegetations. Table 3 summarizes these 11 cases. In the first five patients listed the emboli gave rise to signs and symptoms, thereby constituting a definite clinical picture. For purposes of clinical correlation these cases are designated as group one. The next six patients in table 3, designated as group two, are those in whom there was also premortem embolization of organs from the valvular vegetations, but the signs and symptoms of these emboli were masked by a more primary and symptom-causing disease, principally neoplasm. The remaining 67 patients of the total 78 are designated as group three; in these, either there were no emboli arising from the vegetations, or, if organs contained emboli, there was the coexistence of another potential source for emboli in addition to the valvular vegetations.

TABLE 4

Organs Affected by Emboli Arising from Valvular Vegetations of Nonbacterial Thrombotic Endocarditis

Organ	Group 1: 5 Cases	Group 2: 6 Cases
Brain	4	3
Spleen	3	4
Kidneys	3	5
Heart	1	0
Bowel	2	0
Skin	1	0
Extremities	0	1

Under the column "organs infarcted" in table 3, lungs are enclosed in parentheses in four cases because they are not considered to have been embolized from the valvular vegetations. In one case there was a thrombus arising in a pulmonary artery, in one case the leg veins contained thrombi, and in two cases the leg veins were not searched for thrombi.

Organs Affected by Emboli: As seen in table 4, the organs most commonly affected by emboli were the brain, the spleen and the kidneys.

Involvement of the spleen in all seven cases was without recognized symptoms or signs. In none of the eight cases with embolization of the kidneys were there obvious localizing symptoms, although microscopic

hematuria was found in four of these. When vessels of the brain were involved, by contrast, clinical evidence was usually found, varying from transitory defects in the attention, sensory, motor or speech fields to definite evidence of cerebral infarction. Transitory phenomena occasionally preceded the onset of marked hemiplegia or other neurologic findings, the more pronounced findings possibly occurring as infarction followed further embolization. Without question, the most clinically significant emboli were those involving the brain, as they caused or contributed directly to the patient's death in all of the seven cases so involved.

Associated Clinical and Autopsy Findings: A summary of the most constantly associated clinical and autopsy findings in the 78 patients in this series is presented in table 5.

TABLE 5

Associated Clinical and Autopsy Findings in 78 Patients

Group	Patients	Heart Failure	Irregular Rhythm	Cancer	Other Thromboses
1	5	5	3	2	3
2	6	2	1	4	0
3	67	16	13	22	18
Totals	78	23	17	28	21

CASE REPORTS

Cases 1 and 6 from table 3 are presented to illustrate the two principal types of cases with emboli arising from the valvular vegetations. Case 1 is one in which emboli gave rise to signs and symptoms, constituting a clinical picture. Case 6 is one in which the embolization of organs was masked clinically by neoplasm.

Case 1. This was the second Boston City Hospital admission of a 51 year old white female, admitted 17 days before death because of paralysis of her right leg occurring the day of admission. She had been doing housework at home when her right leg became numb; she was able to walk with a limp, and she did not lose consciousness or complain of pain. Her first admission had been six years earlier, for cholelithiasis and cholecystitis, at which time gall-stones had been removed and a cholecystotomy performed without complications. No cardiac diagnoses had been made during her first admission.

Physical examination on this admission revealed an obese white female lying quietly in bed, in no pain or distress, with her only complaint that she could not move her right leg from the hip downwards. Vital signs were: temperature, 98.8° F.; pulse, 80 and regular; respirations, 18; blood pressure, 180/100 mm. of Hg. On neurologic examination she appeared jovial and giggled easily, with a euphoric mental state. There was spasticity of her right leg, with unsustained clonus. The right plantar reflex was abnormal; the biceps and triceps reflexes on the right were increased in speed and extent of response. There were no other unusual neurologic findings. Her heart was slightly enlarged, without murmurs. Her chest was clear



FIG. 1. *Case 1.* Free edge of mitral valve with large adherent thrombus on auricular surface. The point of actual adherence of the thrombus is at the indented area of the valve. Friability of the thrombus is suggested by its loose, irregular structure. Postmortem clot showing layering of cells is present at the far left. Cellular reaction in the valve cusp is chiefly that of lymphocytes. Hematoxylin and eosin stain, × 80.

to auscultation; her liver was palpable 5 cm. below her right costal margin and was nontender.

Laboratory examinations included the following: The urine was acid, with a specific gravity of 1.013; there was no albumin or sugar. The sediment contained rare red blood cells and rare white blood cells per high power field, without casts. The hemoglobin was 100% of normal; the white blood count was 10,000 per cubic millimeter, with a normal differential. The Hinton test was negative; the nonprotein nitrogen, 26 mg.%. A blood culture drawn on admission was negative. A lumbar puncture revealed a clear fluid under an initial pressure of 210 mm. of water, a final pressure of 105 mm. There were 4 red blood cells and 1 lymphocyte per cubic millimeter; the protein content was 13 mg.%.

During her first five days in the hospital there was no important change in her condition; her temperature ranged between 98.8° and 100° F., with one rise to 101° and a fall to 99° F. within four hours. The white blood count on the fifth day was 6,600 per cubic millimeter. On the sixth hospital day she began to complain of pain in her right upper quadrant, and she vomited several times. She was described as agitated and uncoöperative, requiring sedation. Her complaints of abdominal pain abated; during the next week she gradually became disoriented, and no explanation could be found. Largely because of these changes she was transferred to the neurologic service on the thirteenth day. At that time she was described as irritable, crying easily, in contrast to her earlier moods. Laboratory studies were repeated; the urine was yellow, acid; specific gravity, 1.012, with a trace of albumin. The sediment now contained 50 to 60 white blood cells per high power field; no red blood cells or casts were found. The nonprotein nitrogen was 61 mg.%; a blood culture again showed no growth. An electrocardiogram showed normal sinus rhythm and no apparent myocardial abnormality. On the fourteenth day she developed slight dyspnea, and râles were heard at the bases of her lungs; she was considered to be in mild cardiac decompensation. At that time a cardiac consultation was obtained; the examiner found the electrocardiogram now to show evidence of a myocardial infarction. Her blood pressure had fallen to 140/90 mm. of Hg; her heart sounds were described as having taken on a softer quality, and an apical systolic murmur was now noted. Her liver was tender for the first time, with no apparent increase in size. No embolic phenomena were observed; two blood cultures revealed no growth. On the fifteenth hospital day, however, petechiae were observed over the flexor surface of the left wrist, and the tip of the fifth finger of the left hand became discolored and was considered to have been affected by an embolic process. Later in the day the third and fourth fingers of the right hand became similarly affected. For the first time she complained of moderately severe substernal pain. Two blood cultures again revealed no growth. A catheterized specimen of urine contained many white blood cells in the sediment, and for the first time since admission 5 to 6 red blood cells were present in each high power field. On the sixteenth hospital day she lapsed into coma; petechiae were observed over the outer aspect of her left hip. Her blood pressure was now 120/80 mm. of Hg, her temperature ranging between 99 and 100° F. Sulfadiazine therapy was begun, but she died quietly the morning following. Throughout her hospital course no findings referable to her leg veins had been obtained.

Autopsy: At autopsy a carcinoma of the stomach was found which had metastasized to the liver and to portal and mediastinal lymph nodes. Multiple embolic infarctions of several organs were present; the emboli were considered to have arisen from vegetations on the heart valves. The line of closure and the auricular surface of the mitral valve contained three white-gray, friable vegetations averaging 1.0 by 0.8 by 0.6 cm. The aortic valve contained two similar vegetations on the corpora arantii. The tricuspid valve contained a single 2 mm. vegetation on its auricular aspect. There was no heart disease other than arteriosclerosis of the cor-

onary arteries. The valves were not grossly deformed; the vegetations contained no bacteria on smear or gram stain, or in histologic preparations. Cultures of heart blood and of cardiac vegetations were without growth. Microscopically the heart valves contained focal fibrocollagenous areas of degeneration, over which were adherent thrombi of fibrin and blood cells. There were no Aschoff's bodies in the heart, and no stigmata of rheumatic valvular deformities.

In other organs, in addition to tumor in the areas listed, there were the embolic infarctions. Petechiae were present in the skin, scalp, and serosa of the bowel. Infarctions and petechiae were found extensively in the brain, in the region served by the left anterior cerebral artery chiefly, but also in the anterior and posterior gyral regions, the cerebellum, and the cerebral cortex generally. There were infarctions in the spleen and kidneys; an embolus was demonstrated in the left circumflex coronary artery, with multiple old and recent infarctions of the myocardium. Emboli were present in small branches of the pulmonary arteries, with infarctions of the areas served by the affected vessels. The deep venous system of the legs contained thrombi which were considered to be the most probable source of the emboli in the pulmonary arteries. In addition, there were fibrin thrombi in many kidney glomeruli, and in capillaries, venules, and arterioles of the heart, spleen and liver.

Comment: This patient is placed in the clinical group in which embolic infarction of organs constituted the main clinical illness insofar as signs and symptoms were concerned. She entered the hospital with an embolic cerebral episode and, in retrospect, her sudden cerebral symptoms along with the finding of microscopic hematuria were features suggesting that multiple embolization had occurred. During her hospital course a cardiac murmur developed, microscopic hematuria recurred, and toward the end of her life skin petechiae and sudden occlusive vascular phenomena of her fingers became manifest. Other than a brief episode of abdominal pain, there were no symptoms referable to her gastric carcinoma. For the last two days of her life the clinical diagnosis was subacute bacterial endocarditis.

The unusual features of this case are the embolism of the coronary artery, which is a rare event, and the presence of fibrin thrombi in glomeruli, capillaries, arterioles and venules. Such fibrin thrombi were present in two of the 78 cases in this series; these are considered to represent a nonspecific finding, such as that reported by Jones and Loring,[7] who found them in 3.6% of a series of routine autopsies. There was no evidence for the other diseases which one considers with this finding, such as thrombocytopenic purpura, lupus erythematosus and bacterial endocarditis.

Case 6. This 75 year old white widow was admitted to the Boston City Hospital with a 10 month history of epigastric pain. She described the pain as dull and aching, occurring approximately once each week, unrelated to food intake, and radiating through to her back. In addition, she had noticeably lost weight over the previous six months. Her past history, family history and system review were not contributory.

On physical examination she was a thin elderly white female in no acute distress, with evidence of recent weight loss, and with evident generalized weakness. Her temperature was 98.6° F.; pulse, 80 and regular; respirations, 24; blood pressure, 155/80 mm. of Hg. Her heart was slightly enlarged, with a grade 3 precordial systolic murmur and a normal sinus rhythm. Her chest was clear to auscultation;



FIG. 2. *Case 6.* Mitral valve with small adherent thrombus on auricular surface. There is only slight cellular reaction in the valve, at the point of adherence of the thrombus. Verhoeff's elastica stain, × 15.

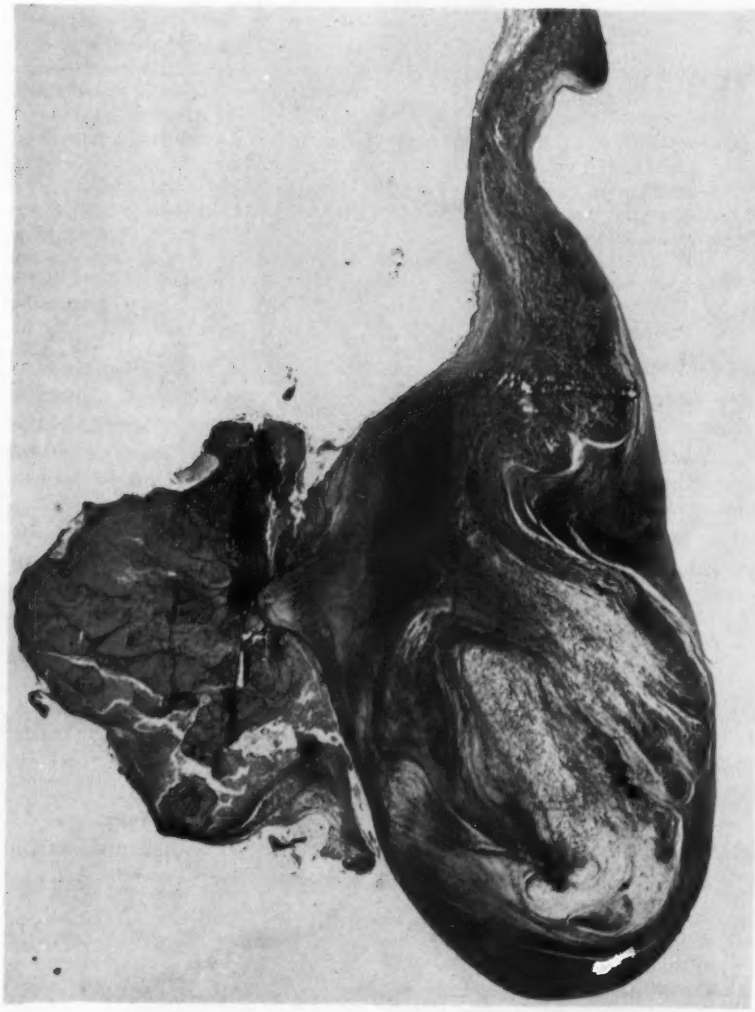


FIG. 3. Mitral valve from an additional case, illustrating adherent thrombus at site of fibrocollagenous nodule of valve. Verhoeff's elastica stain, × 15.

her liver and spleen were not palpable. A large mass was palpated and percussed in the lower abdomen, which was ill-defined, fluctuant and nontender. On pelvic examination this mass was considered to be ovarian in location. A few small lymph nodes were palpated in each inguinal region. There was no edema of the extremities.

On laboratory examination the hemoglobin was 13 gm.%; hematocrit, 37%; white blood count, 7,500 cells per cubic millimeter. The differential count was 85% polymorphonuclears, 12% lymphocytes and 3% eosinophils. The Hinton test was negative; nonprotein nitrogen, 44 mg.%; fasting blood sugar, 120 mg.%; total cholesterol, 182 mg.%; icteric index, 5 units; the stools were negative for occult blood. The urine was acid, with a specific gravity of 1.020; it contained no albumin, sugar or bile, and there were present in the sediment only 3 to 5 white blood cells per high power field.

Her clinical diagnosis was ovarian carcinoma, and she was confined to bed because of weakness. She did well for two days but then began to complain of occasional epigastric and low back pains. On her fourth hospital day her urine showed 2 plus albumin, with 12 to 15 white blood cells and rare red blood cells in the sediment. On her fifth day 2 plus albumin and rare red blood cells were again found in her urine. Her episodes of pain became more severe and frequent, differing slightly in location and character from those which had preceded her hospital admission. On the sixth day her temperature, which had been normal, rose slightly. A blood culture was drawn, which showed no growth, and penicillin therapy was begun, consisting of 400,000 units per day. A white blood cell count on the sixth day was 20,150 per cubic millimeter, with a differential count of 93% polymorphonuclear leukocytes, 3% lymphocytes and 4% monocytes. On the thirteenth hospital day her right leg suddenly became swollen, edematous, painful, and without arterial pulsations from the popliteal region downwards, although good femoral pulsations were present. Her blood pressure became unobtainable, her pulse rapid and weak, and her skin cold and clammy. A lumbar sympathetic block was performed on the affected side and anticoagulants and oxygen were given, but she died within four hours, on her fourteenth hospital day.

Autopsy: At autopsy the chief findings were in the pancreas, the left ovary, the heart, and certain infarcted visceral organs. There was an adenocarcinoma of the pancreas which had metastasized to regional lymph nodes, to the lungs and to the liver. The abdominal mass which had been palpated was found to be a serous cystoma of the left ovary containing 2,500 c.c. of a clear fluid. The heart contained vegetations on the free edges of the mitral and tricuspid valves and on the corpora arantii of the aortic valve. These were multiple gray-white nodules, each less than 3 mm. in diameter. There were no valvular deformities, although microscopically the valves contained focal areas of relatively acellular fibrocollagenous substance, to which were attached thrombi composed of fibrin and blood cells. There were no Aschoff's bodies in the heart. In the kidneys and spleen were small infarctions, and in a secondary artery of the left lower lobe of the lung there was an embolus with infarction of the region served by the vessel. There was an early gangrene of the right lower leg, but no occlusion of the popliteal artery or vein was found. Only the popliteal and femoral areas of the vessels of the right leg were examined.

Comment: The clinical evidence of neoplasm in this case was confirmed at autopsy; in addition, it appeared in retrospect that not all her symptoms of abdominal and back pain were caused by the tumor. The occurrence of microscopic hematuria on two occasions was consistent with embolization of her kidneys and probably contributed to her symptoms. The sudden

vascular involvement of the popliteal artery region was considered to be consistent with embolization of the popliteal artery, but this was not confirmed at autopsy. This case is placed in the second clinical group because the symptoms and signs of neoplasm overshadowed the embolic phenomena.

Discussion

General: The valvular vegetations of nonbacterial thrombotic endocarditis have in the past been of interest chiefly to the pathologist, and the condition has generally been considered to be merely an incidental postmortem finding. However, from a study of the 11 cases in this series in which there was multiple embolization of organs, evidence is considered to exist that the condition may have clinical importance, and this evidence may be summarized as follows: First, in these cases no source for emboli other than the valvular vegetations was found. Second, the nature and multiplicity of vascular lesions in the infarcted organs confirmed their embolic origin. Third, the infarctions were of such age histologically as to indicate that they had been present for a short time before death, and they did not occur, therefore, as terminal phenomena. Fourth, seven of the 11 patients had regular cardiac rhythms at all times, demonstrated both on routine physical examinations and by electrocardiograms, so that an irregular cardiac rhythm giving rise to emboli could not be invoked as a possible source in these cases. Fifth, the auricles in three of the four cases with auricular fibrillation were examined microscopically; there was no gross or microscopic evidence of reaction in the auricular endocardium, such as might have been consistent with preëxisting thrombus.

The vegetations of this condition, then, may be the source of multiple emboli, and, in addition, they have been considered to be of importance in the pathogenesis of bacterial endocarditis, for which evidence has been presented in prior writings.[8, 9, 10] The finding in this series that in 14% of cases the valvular vegetations gave rise to emboli is in apparent contrast to the experience of prior workers, so that an explanation should be sought for this difference. The following points appear to have direct bearing on the question: First, as stated earlier, the early work on this condition dealt with its histologic features, so that no extensive study of its possible clinical significance has been made. Second, as implied above, some of the contrasting experience is apparent only. For example, although Libman originally stated that the condition had no clinical significance,[1] he observed in a later article that the vegetations might occasionally give rise to emboli.[2] Third, and a related point, is that in past years at this institute rare cases of nonbacterial thrombotic endocarditis giving rise to premortem embolic infarction of organs have been recognized at time of autopsy. The frequency of occurrence of such embolization and its possible clinical significance were not appreciated until the cases were reviewed. The same is probably true in other large departments of pathology where complete

routine autopsies are performed, and where adequate records are available. For example, Adams [6] states that he has known for a long period of time that the vegetations may give rise to clinically important emboli. Fourth, the rarity of this condition, as evidenced by only 78 cases among 18,486 autopsies over a 22 year period at this institute, has not made it possible for any one clinician or pathologist to gain personal experience with a large number of cases.

Pathogenesis: There appears to be a definite relationship between a preexisting focal nonspecific valvular deformity as a nidus for thrombus formation, and the superimposition of nonbacterial thrombotic endocarditis upon such a lesion. The pathogenesis of this condition is considered to be the formation of a thrombus, formed from blood elements within the cardiac chambers, upon a focally or diffusely deformed valve. Consistent with this theory of pathogenesis are certain findings in a series of 1,000 random adult autopsies on persons without rheumatic heart disease.[11] Of this group, 50.2% had gross deformities of the heart valves or endocardium, which were often considered to be within the range of normal degeneration and variation for the patient's age. Of those hearts with deformities, 99% of the abnormalities involved the valves and endocardium of the left side of the heart. Similarly, in the present study of nonbacterial thrombotic endocarditis, 97% of the vegetations occurred on valves of the left side of the heart. It is evident that many persons coming to autopsy have focal valvular deformities of a nonspecific type, yet in only relatively few does nonbacterial thrombotic endocarditis develop. Whether certain factors associated with illness favor the formation of valvular and other vascular thrombi is not clear from the material at hand. The presence of a hypercoagulable state in many diseases, favoring such thrombus formation, should be considered in view of the large number of associated thrombi in cases in this series, and in view of the known association of multiple venous thrombi with carcinomatosis and certain types of cancers.

Rôle of Antibiotic Therapy: The possibility that the endocardial vegetations of this condition represented sterilized vegetations of bacterial endocarditis in patients given antibiotics before death was investigated and did not prove to be the case. Of the 78 patients, 46 (59%) had received antibiotics or sulfa drugs, made up of two of the five patients in group one, three of the six in group two, and 41 of the 67 in group three. A comparison of the anatomic findings in the heart valves and vegetations in those patients who had received antibiotics as compared with those who had received none revealed no significant differences, and no indications that the vegetations had ever been bacterial in origin. In addition, in many cases antibiotics had been given for only a few hours before death, so that, all evidence considered, it appeared highly improbable that antibiotics had altered preëxisting bacterial vegetations.

Anatomic Differentiation: The important differentiation of nonbacterial

thrombotic endocarditis is from bacterial and rheumatic endocarditis showing some degree of activity, and from atypical verrucous endocarditis of Libman-Sacks. Generally speaking, this presents no difficulty. The main feature is the lack of cellular reaction in the involved valve in nonbacterial thrombotic endocarditis in contrast to the other types.

1. Acute bacterial endocarditis may be found with little cellular reaction deep within the valve, away from the vegetation, but it is differentiated by large valvular vegetations with necrotic or ulcerative bases in which the acute inflammatory cell response at the valve surface is obvious. In addition, there may be a distinctive clinical picture and the finding of a primary site for the entrance of bacteria into the blood stream.

2. In subacute bacterial endocarditis with bacteremia there are positive premortem blood cultures, a highly cellular reaction in the affected valve, and the finding of bacteria in the vegetations on gram stain, histologic section, and on culture.

3. Subacute bacterial endocarditis in the bacteria-free state, or in the healing state following antibiotic therapy, reveals a highly cellular valve reaction, often with healing ulceration of the valve, and the finding of bacteria within the vegetations. There are deposition of lime salts and layering of fibrin as healing occurs in the vegetations, and if fibrin is attached to the valve it is usually present over an extensive valve surface.

4. Active rheumatic endocarditis is differentiated by the findings of large gross endocardial lesions, tending to involve the left auricular endocardium, associated stigmata of rheumatic activity in the joints and pericardium, the presence of Aschoff's bodies on microscopic examination, and, again most important, a cellular valvular reaction.

5. The atypical verrucous endocarditis of Libman-Sacks is differentiated by the presence of lupus erythematosus, an associated pericarditis, involvement of the valve pockets, vascular lesions in other organs, particularly the glomeruli of the kidneys, and a cellular reaction in the valve, with fibrinoid lesions.

6. Healed bacterial endocarditis and healed rheumatic endocarditis often show a degree of residual cellular reaction in the valve, and in the latter case stigmata of healed rheumatic valvulitis as described by Gross [12, 13] may be found. The important conditions from which healed nonbacterial thrombotic endocarditis and degenerative type nonbacterial thrombotic endocarditis must be differentiated are healed bacterial and healed rheumatic endocarditis. This differentiation cannot be made with the same degree of certainty as in the other conditions listed. The best criteria seem to be: (1) that the diagnoses of healed and degenerative types of nonbacterial thrombotic endocarditis are not made in the presence of rheumatic heart disease; (2) that the bacterial vegetations tend to be of greater extent and number than those of the nonbacterial thrombotic type, and often contain layers of calcium.

Clinical and Pathologic Features: Nonbacterial thrombotic endocarditis does not occur only in terminal wasting diseases, as is apparent from its occurrence in this series in such conditions as heart failure, pneumonia, pyelonephritis, glomerulonephritis, and in a healed form. It does not occur solely in the elderly, as is evident from the fact that six of the 78 patients in this series were under the age of 40. It has been stated in the past that the condition does not occur only in invariably fatal diseases.[4] Some evidence for this view is obtained from the finding in this series of healed vegetations in three cases. There are many difficulties in assigning this as definite evidence, however, not the least of which is that of attributing an etiology to the endocardial lesions when there is no conclusive history and only the healed form is encountered.

In contrast with the experience of other workers, rheumatic valvular deformities were not the principal condition in this series upon which the lesions were superimposed. Arteriosclerotic heart disease was clearly the predominant condition. In 10% of cases there was no anatomic heart disease, although on microscopic examination all the affected valves contained focal deformities.

The separation of the patients in this series into three clinical groups is a purely arbitrary one, in the hope that an analysis of the groups may allow some diagnostic clinical considerations. The first group, in which embolization of organs constitutes the chief clinical picture, may permit of premortem diagnosis. In a patient with cardiac decompensation and evidence of embolization of several organs, the important differentiation is between nonbacterial thrombotic endocarditis, bacterial endocarditis, and mural thrombi of the cardiac chambers. In the second group, in which embolization is at least partially masked by a more primary disease, diagnosis is more difficult, and may be considered when a patient in the elderly age group confined to bed develops symptoms consistent with embolization of organs, and which do not constitute a phase of the natural history of the primary disease. Adams [6] has stated that a cerebral vascular embolus in a patient with nonbacterial thrombotic endocarditis may, in his experience, constitute the initial hospitalizing illness when an occult carcinoma is present. In this series, this was true in two of the 28 cases with neoplasm.

Diagnosis in the third group, in which there is no embolization of organs, and in which the valvular lesions constitute an incidental finding at autopsy, is probably not possible. In none of the three clinical groups was the finding of a changing cardiac murmur of consistent diagnostic aid, despite its presence in case 1 of group 1.

Once the diagnosis is made there is no specific therapy at the present time. The chief value of diagnosis, therapeutically speaking, is in determining that involvement of cerebral vessels, if present, is due to an embolic process, for recent trends in therapy of cerebrovascular accidents are different for early embolic lesions than for other forms of vascular involve-

ment.[14] With attention to the clinical importance of nonbacterial thrombotic endocarditis, further studies may reveal causative conditions amenable to therapy. Allen has suggested the possible rôle of such factors as vitamin C deficiency, and, if predisposition to vascular thromboses is found to play an important rôle, anticoagulant therapy will be indicated.

Summary and Conclusions

1. An autopsy and clinical study of 78 cases of nonbacterial thrombotic endocarditis are presented. In 11 cases (14%) emboli were found which were considered to have arisen from the valvular vegetations and to have caused or contributed to the patient's death.

2. The pathogenesis of the vegetations is considered to be the occurrence of thrombi formed from blood within the cardiac chambers upon nonspecific areas of focal fibrocollagenous degeneration of valves. When embolization occurs, it is considered to be the result of a portion of adherent thrombus breaking off into the circulation.

3. The most commonly associated diseases in this series were cancer (36%), heart failure (30%) and vascular thromboses (27%).

4. The chief therapeutic value of clinical recognition of the condition at the present time is in differentiating embolic cerebral vascular disease from hemorrhage and thrombosis, and in directing attention to associated and perhaps causative conditions.

5. It has been repeatedly stated in the past that nonbacterial thrombotic endocarditis is an insignificant finding at autopsy. Evidence is presented in this series that such is not always the case, and with an awareness of the possible importance of this condition, it deserves further attention. From further studies may come information of value in prevention and treatment.

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Summario in Interlingua

Septanta-octo casos de endocarditis thrombotic nonbacterial occurreva inter 18.486 necropsias al Hospital del Citate de Boston in le curso de un periodo de 22 annos. Esseva trovate indicios necroptic que in 11 casos (14%) le vegetationes valvular habeva producite embolos ante morte. Le organos principalmente afficite esseva le cerebro, le splen, e le renes. In un studio de iste casos un division arbitrari del patientes esseva effectuate super le base del presentia o absentia de embolos liberate per le vegetationes valvular e del grado de manifestationes clinic producite per le embolos. Gruppo 1 includeva cinque patientes in qui embolisation e infarcimento de organos habeva occurrite e in qui le resultante signos e symptomas habeva representate le principal aspectos clinic. Gruppo 2 includeva sex patientes in qui embolisation e infarcimento de organos habeva occurrite sed in qui le resultante signos e symptomas habeva representate aspectos clinic de importantia secundari in comparation con le manifestationes de un morbo plus primari, usualmente de character neo-

plasmatic. Gruppo 3 consisteva del remanente 67 patientes in qui le endocarditis esseva solmente un constatation necroptic incidental.

Pathologicamente le vegetationes esseva componite de thrombos sanguinee que se habeva formate super deformitates valvular. Subjacente alterationes valvular o endocardial esseva demonstrate in omne casos per medios microscopic in le loco del vegetationes. Illos esseva usualmente del nonspecific typo degenerative fibrocollagenic que se trova in circa 50% del patientes necropsiate sin rheumatic morbo cardiac. In le presente studio nulle responsa esseva obtenite al question proque un parve procentage de patientes con nonspecific deformitates valvular ex le grande numero de patientes con alterationes valvular se distingueva per le disveloppamento de endocarditis thrombotic. In le gruppo de 78 patientes, le plus commun conditiones associate esseva neoplasma (36%), disfallimento cardiac (30%), e altere thromboses vascular (27%).

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STUDIES IN PSYCHIC FATIGUE. I. PHYSIOLOGIC FINDINGS *†

By Benjamin Kissin, M.D., Irwin Jaffe, M.D., Philip Rosenblatt, M.D., Charles S. Byron, M.D., F.A.C.P., and Ira Freiman, M.D.,
Brooklyn, New York

Psychic fatigue is not a distinct clinical entity but is generally a symptom of some underlying psychiatric condition. The syndromes which result in psychic fatigue include, among others, anxiety states and depressions. There is, however, a large group of patients with psychic fatigue who do not fall easily into any major psychiatric classification. These patients may show elements of anxiety or depression, but their fatigue seems to be out of all proportion to the severity of the more definite symptoms. In the past, this syndrome was labeled "neurasthenia." More recently, the tendency has been to make a more definite diagnosis (anxiety neurosis or depression), with fatigue as the dominant symptom.

Even though patients with psychic fatigue do not constitute a homogeneous group psychiatrically, the symptomatic predominance of fatigue suggests that there may be some underlying physical common denominator. The symptomatology of psychic fatigue is so markedly somatic that many workers have sought physiologic findings that might characterize the condition. Alexander and Portis [1] were the first to present a physiologic defect —the flattened intravenous glucose tolerance curve—which appeared to be characteristic for patients with psychic fatigue. They found that this curve could be reversed by first giving atropine, and deduced from this that the increased glucose tolerance was due to increased vagotonia.

Tintera,[2] in a clinical review on the hypoadrenocortical state, described a large group of patients who were apparently comparable to patients with psychic fatigue. In his terminology these are patients with acquired hypoadrenocorticism as the result of prolonged stress. The list of chief complaints—fatigue, nervousness and irritability, and mental depression—makes it most likely that in a more psychiatrically oriented study these patients would be labeled as sufferers from "neurasthenic syndrome." Consequently, the functional changes described are of extreme interest to us. These are: (1) low basal metabolic rate; (2) on x-ray, a J-shaped stomach with visceroptosis; (3) eosinophilia; (4) increased glucose tolerance (low flat curve); (5) relative lymphocytosis, and (6) low urinary 17-ketosteroids.

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From the Central Medical Group of Brooklyn, Brooklyn, N. Y.
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Requests for reprints should be addressed to Benjamin Kissin, M.D., Central Medical Group of Brooklyn, 345 Schermerhorn Street, Brooklyn 17, New York.

From these and other findings, Tintera concluded that these patients suffered from adrenal cortical insufficiency and autonomic nervous system imbalance as well.

Clinical observations made by the authors on patients with psychic fatigue have also led to the conclusion that this condition is characterized by disturbances in the endocrine as well as the autonomic nervous system. Consequently, a survey of these two systems was undertaken to determine more exactly the nature of these disturbances and to establish, if possible, a theoretical basis for explaining them.

Methods

Nineteen patients in whom psychic fatigue was the major symptom were the subjects of the experiment. All the patients underwent complete medical examinations, including chest plates, complete blood counts, urine analyses and electrocardiograms. No patient with known organic disease was included in the group. All patients were also given psychiatric interviews, and those with overt psychiatric conditions (acute anxiety states, psychoses, acute depressions, etc.) were excluded.

The experiment was divided into two parts. The first part included a battery of autonomic nervous system tests to reveal evidence of imbalance. The second part was an endocrinologic survey, including studies of the function of the adrenal cortex, the thyroid gland, the gonads and, indirectly, the anterior pituitary gland.

A. *Tests of Autonomic Nervous System Function:*

1. Intravenous Glucose Tolerance Test.

The method used in this experiment was that of Lozner et al.[3] Fifty cubic centimeters of 50% glucose solution were injected intravenously, and blood glucose determinations were done at fasting, 15, 30, 60, 120, 180 and 240 minute intervals.

Criteria for increased glucose tolerance were taken from the curve published by Lozner et al., and were based on one or both of the following:

(a) The finding on the 30 minute specimen of a blood glucose level lower than 105 mg.%. This figure is arrived at by subtracting the standard deviation from the mean (145 mg.%). Levels below 105 mg.% indicate a curve with an abnormally rapid rate of decline.

(b) A value of below 65 mg.% on any specimen. Values below this level are generally considered hypoglycemic, an indication of increased glucose tolerance.

Glucose tolerance is a function of the endocrine system and the liver as well as of the autonomic nervous system. However, the finding by Alexander and Portis that the flat glucose tolerance curve of psychic fatigue is reversed by atropine suggests that the defect is due mainly to autonomic

imbalance. It is for this reason that we include it here. We shall consider the other factors in the main discussion.

2. The Cold Pressor Test.

This was done after the method of Hines and Brown.[4] The blood pressure was determined at one minute intervals during a baseline rest period, and then for a two-minute period with the patient's forearm plunged into a bucket of ice water. According to Igersheimer,[5] the lower limit of normal response, established by subtracting the standard deviation from the mean, is an increase of 12 mm. systolic and 15 mm. diastolic in males, and of 8 mm. systolic and 11 mm. diastolic in females.

3. The Cardiorespiratory Reflex (CRR).

This test is based on the physiologic finding that during *deep* inspiration there is a vagus reflex which tends to slow the pulse.[6] This is in contradistinction to normal inspiration, which actually increases the pulse rate. In the test as performed, the patient's pulse rate is first counted for 15 seconds. The patient is then instructed to take a deep breath and hold it, and the pulse is immediately counted for 15 seconds. The entire procedure is then repeated.

The decrease in pulse rate due to deep inspiration is calculated by subtracting the mean pulse rate during deep inspiration from the mean pulse rate at rest, and then relating the difference to the resting pulse rate $\left(\frac{N - DI}{N}\right)$. Kissin,[7] in a study on 100 normals to be reported elsewhere, found that over 90% of his subjects showed a decrease in pulse rate of less than 10%. A decrease in pulse rate of more than 10% was considered indicative of increased vagotonia.

B. *Tests of Endocrine Function:*

1. Tests of Adrenal Cortical Function.

(a) Urinary 17-ketosteroids. These were determined by the method of Reddy et al.[8] The limits of normal for males are 10 to 15 mg. per 24 hour urinary excretion, and for females, 4 to 8 mg. per 24 hour urinary excretion.

(b) Urinary 17 hydroxycorticoids. These were determined by the method of Zimmerman.[9] The limits of normal for males are 3.5 to 10 mg. per 24 hour urinary excretion, and for females, 3 to 7 mg. per 24 hour urinary excretion.

(c) The ACTH eosinophil test.[10] A drop of over 50% in the eosinophil count four hours after the injection of 25 mg. of ACTH was considered normal.

(d) The adrenalin-eosinophil test.[11] The present significance of this test is very much in doubt. It is probable that it is *not* a test of anterior pituitary function but rather of the adrenal cortex. According to Thorn,[12]

the adrenalin effect is proportional to the amount of circulating adrenal cortical hormone, and may occur even in the absence of the anterior pituitary gland.

The test was done by calculating circulating eosinophils before, and two hours and four hours after the injection of 0.3 c.c. of adrenalin, 1 : 1000. A drop of 50% or more at any time was considered normal.

2. Tests of Thyroid Function.

(a) The basal metabolic rate. Values of plus 10% to minus 10% were considered normal.

(b) Serum protein-bound iodine.[13] Normal values are 4 to 8 gamma%.

(c) Serum cholesterol. Normal values are 180 to 260 mg.%. Levels above 260 mg.% are suggestive of hypothyroidism.

3. Tests of Gonadal Function.

(a) In women—gonadotropins and estrin: These were determined according to the methods of Klinefelter et al.[14] and Allen and Dorsey,[15] respectively. According to these technics, in normally menstruating women the urine gives a negative reaction for gonadotropins and a positive one for estrin. After the menopause these findings are reversed.

(b) In men: Very low values of the urinary 17-ketosteroids were considered suggestive of testicular hypoactivity as well as of adrenal cortical underactivity, since in males these hormones are produced almost evenly by the testes and adrenal cortex.

TABLE 1

No.	Case	Sex	Age	Glucose Tolerance							Cold Pressor Increase		CRR Δ/Resting Pulse
				F	15	30	60	120	180	240	Syst.	Diast.	
1	G. A.	F	38	65	180	145	70	65	65	65	10	15	− 9/86
2	E. H.	M	33	70	150	100	75	75	85	85	20	20	+ 5/61
3	C. N.	F	44	63	200	150	102	70	80	68	20	13	−10/64
4	S. P.	F	31	55	160	145	60	60	60	55	5	5	−13/82
5	A. S.	M	40	90	135	105	75	90	90	90			
6	H. G.	F	52	70	230	185	180	46	67	75	0	5	−16/84
7	L. S.	F	49	82		85	80	75	85	85	7	15	+ 8/68
8	E. E.	F	40	95	200	100	75	75	90	100			
9	R. G.	F	40	96	180	100	95	97	95	93	10	10	−20/90
10	L. A.	M	35	100	—	115	90	95	95	90	22	30	0/72
11	G. F.	F	57	105	—	218	169	110	85	90	8	5	0/80
12	E. T.	F	41	70	—	85	75	70	65	75	25	22	− 4/71
13	J. M.	F	48	100	—	110	75	90	95	103	10	20	−18/88
14	R. B.	F	40	65	—	65	55	60	80	80	3	8	−18/82
15	C. L.	F	47	94	200	135	82	85	93	91			
16	P. K.	F	47	85	—	180	125	90	85	83	7	5	− 6/72
17	A. R.	M	26	75	150	100	86	70	75	75	22	23	−12/76
18	M. R.	F	35	85	—	90	90	85	60	60	30	30	
19	A. S.	F	32	75	190	220	165	85	75	80	12	10	− 6/76
Per Cent Abnormal				69%							50%		53%

TABLE 1—*Continued*

No.	Case	Sex	Age	17Ks	17OH	ACTH Eosinophil		Adrenalin Eosinophil		BMR	PBI	Cholesterol	Prolan	Estrin
						Pre	Post	Pre	Post					
1	G. A.	F	38	3.9	4.8	60	0	38	0	− 6	3.0	170	Neg.	Pos.
2	E. H.	M	33	13.1	2.0	100	20	100	15	−11	3.0	150	Neg.	Neg.
3	C. N.	F	44	10.0	3.0	300	75	205	50	−24	3.3	190	Pos.	Neg.
4	S. P.	F	31	11.0	4.0	62	0	50	50	−31	4.0	150		
5	A. S.	M	40	6.8	2.7	100	0	70	100	−12	4.0	252		
6	H. G.	F	52		10.0	50	0	50	0	+10	4.6	255		
7	L. S.	F	49			25	0				5.0	170	Pos.	Neg.
8	E. E.	F	40	4.0	3.8	50	0	110	70	−32	3.8	160	Neg.	Neg.
9	R. G.	F	40	5.0	1.6	100	25	75	150	−11	6.2	220	Neg.	Neg.
10	L. A.	M	35	7.0	3.0	100	45			−15	4.0	175		
11	G. F.	F	57		3.8	30	0				3.6	160		
12	E. T.	F	41	6.1	3.0	50	25	25	25	− 7	4.0			
13	J. M.	F	48	7.0	3.0	300	50	100	150	−26	5.0	200		
14	R. B.	F	40	12.0	3.0	87	100	75	0	−26	4.8	205	Neg.	Neg.
15	C. L.	F	47			300	110	200	75	0	5.1	185	Neg.	Pos.
16	P. K.	F	47	10.0	2.3	150	6	25	37	− 8	4.0	200		
17	A. R.	M	26	4.0	3.0	125	20	250	200	− 9	4.4	203		
18	M. R.	F	35			150	50	100	50	−23			Neg.	Neg.
19	A. S.	F	32			75	25	100	25	−10			Neg.	Pos.
Per Cent Abnormal				46%	67%	5%		50%		65%	59%	0%	63%	

RESULTS

The results are listed in table 1. The figures designate percentage of abnormalities in terms of the criteria established in the previous section.

A. *Autonomic Nervous System:*

1. Intravenous glucose tolerance.

Thirteen out of 19 (or 69%) of our patients showed increased glucose tolerance according to the criteria described. Six patients had normal curves. None of the patients showed evidence of decreased glucose tolerance.

2. Cold pressor test.

Eight out of 16 patients tested (or 50%) showed blood pressure increases less in either systolic or diastolic, or both, than the lower limit of normal as described.

3. Cardiorespiratory reflex.

Eight out of 15 patients tested (or 53%) showed a decrease in pulse rate of more than 10%.

B. *Endocrine System:*

1. Adrenal Cortical Function.

(a) Urinary 17-ketosteroids. In women, only two of nine of the patients (or 22%) showed a low level of urinary 17-ketosteroids. In the males, on the other hand, three out of four (or 75%) showed markedly

lowered figures. The latter were taken to be more significant of testicular deficiency.

(b) Urinary 17 hydroxycorticoids. Six out of 11 of our female patients (or 55%) showed levels at or below the lower limit of normal. In the males, on the other hand, four out of four (or 100%) showed levels well below the lower limit of normal.

(c) ACTH eosinophil tests. Eighteen out of 19 patients (or 94%) gave normal reactions. However, this by no means indicates normal adrenal cortical activity. The ACTH eosinophil test is a measure of adrenal cortical *capacity* rather than *activity*. It would appear from this and the previous tests that in psychic fatigue the adrenal cortex is capable of normal activity but actually functions below its full capacity. This would tend to indicate underactivity of the anterior pituitary gland as the actual explanation of the adrenal cortical hypoactivity.

(d) The adrenalin-eosinophil test. Eight out of 16 patients (or 50%) gave negative adrenalin-eosinophil responses. Since a negative adrenalin-eosinophil response indicates a low level of circulating adrenal cortical hormone, in the presence of a positive ACTH-eosinophil response it signifies that the adrenal cortex is functioning at only part of its total capacity. This latter condition is usually secondary to underactivity of the anterior pituitary. Consequently, a negative adrenalin-eosinophil response in the presence of a positive ACTH-eosinophil response is suggestive of anterior pituitary underactivity.

2. Thyroid Function.

(a) Basal metabolic rate. Eleven of 17 of the patients (or 65%) had basal metabolic rates of minus 10% or lower. Of the six who did not, four ranged between minus 6% and minus 9%, one was zero and one plus 10%.

(b) Protein bound iodine. Ten of 17 of our patients (or 59%) had a PBI at or below the lower limit of normal. One was above the upper limit of normal, while the others were fairly random within the normal range.

(c) Cholesterol. None of 17 patients (or 0%) gave values over 260 mg.%. The absence of high cholesterol levels in the presence of low basal metabolic rates and low PBI's is strongly suggestive, according to Thorn and Forsham,[16] of hypometabolism secondary to pituitary insufficiency rather than to primary hypothyroidism.

3. Gonadal Function.

(a) Females—gonadotropin-estrin test. Only one of our women tested (case 7) was postmenopausal. She gave the usual prolan (+), estrin (—) result. Of the nine premenopausal women, three (33%) gave normal results, prolan (—), estrin (+), while six (67%) gave abnormal results. Of this last group, one who was approaching menopause gave the menopausal pattern, prolan (+), estrin (—), while the five younger women gave an atypical pattern, prolan (—), estrin (—). Both these patterns represent

hypogonadism, primary and secondary, respectively. The menopausal pattern, prolan (+) estrin (—), signifies a primary inactivity of the ovaries. The atypical prolan (—) estrin (—) pattern characterizing the majority of our women patients is indicative of ovarian hypoactivity secondary to underactivity of the anterior pituitary gland.

(b) Males—urinary 17-ketosteroids. Three of the four men tested gave 17-ketosteroid values that were so low (7, 6.8, 4) that they could hardly be explained solely on the basis of adrenal cortical underactivity. These are figures one might expect in Addison's disease. Since there is evidence of at least some adrenal cortical function here, these very low 17-ketosteroid levels are strongly suggestive of testicular hypofunction.

Discussion

A. *Autonomic Nervous System:*

The findings on the glucose tolerance, the cold pressor and the cardiorespiratory tests indicate that in psychic fatigue there is an imbalance in autonomic nervous system activity. This expresses itself as both parasympathetic overactivity (glucose tolerance and CRR) and sympathetic underactivity (cold pressor). Portis and Alexander's finding that the characteristically flat glucose tolerance curve could be reversed by atropine is further evidence of this fact, as are the various clinical manifestations of the condition (gastrointestinal spasticity, hypotension, etc.).

As we have previously stated, a valid interpretation of the glucose tolerance curve must take into consideration, in addition to the autonomic nervous system, the elements of endocrine and liver function. As far as the latter is concerned, there was no clinical or laboratory evidence in our study of hepatic disease in any of our patients. On the other hand, we know that most of our patients had a functional deficiency of the adrenal cortex and thyroid glands, both of which are intimately involved in glucose tolerance. Undoubtedly, the final curves were, in part, determined by the adrenal cortical and thyroid deficiencies which would tend to flatten them. But the criteria for abnormality which we have established would appear to depend more on the rate of mobilization of insulin (i.e., parasympathetic activity) than on adrenal or thyroid activity, since they involve the rate of decline of the curve rather than its general level. For this reason, and because the curves can be corrected with atropine, we may assume that the increased glucose tolerance in the neurasthenic syndrome is partially due to endocrine influences but mainly due to increased vagotonia.

This impression is, of course, supported by the other test data, i.e., the cardiorespiratory and the cold pressor responses, both of which indicate a shift in autonomic nervous system activity toward the parasympathetic side. These experimental physiologic findings tend to corroborate the clinical impression of generalized vagotonia which these patients give.

B. *Endocrine System:*

The test data in our study on neurasthenia appear to indicate a functional underactivity of the entire endocrine system. The evidence for a functional adrenal cortical insufficiency is most direct and unequivocal (low 17-ketosteroids and 17-hydroxycorticoids). The normal ACTH-eosinophil responses do not speak against adrenal cortical hypofunction, but do establish it as functional rather than organic. This, together with the high percentage of negative adrenalin-eosinophil tests, suggests that the primary functional defect is in the anterior pituitary rather than in the adrenal cortex.

The data on gonadal function likewise indicate a secondary hypofunction rather than a primary one, tending again to incriminate the anterior pituitary. The (—) estrin (—) prolan pattern in our menstruating women is characteristic of ovarian deficiency secondary to anterior pituitary deficiency. The data on the male patients unfortunately shed no real light on this aspect.

The data on the thyroid tests, i.e., the low and normal cholesterol levels in the presence of low basal metabolic rates and PBI's, strongly suggest that the thyroid underactivity is also secondary to pituitary hypofunction. Unfortunately, the definitive experiment of testing the radioactive iodine uptake of the thyroid after the administration of thyrotropic hormone could not be done. However, the pattern of hypothyroidism displayed, plus the presence of secondary adrenal cortical and gonadal hypofunction, suggests the likelihood that the underactivity of all three target glands is secondary to underactivity of the anterior pituitary.

C. *General Considerations:*

This study would appear to have established neurasthenia as a physiologic entity if not a psychologic one. The consistency with which the great majority of our patients show some or all of the stigmata of vagotonia and panendocrine deficiency provides an adequate physiologic explanation for the clinical symptomatology of which these patients complain.

Anatomically, the specific area which appears to be implicated is the hypothalamus. This region is generally considered to be the control center of the autonomic nervous system as well as the neurogenic organ which controls the activity of the anterior pituitary gland. We do not mean to imply that there is organic disease of the hypothalamus in these patients; the evidence is very much against that. On the other hand, there does appear to be a functional imbalance in the overall activity of that brain center. The exact cause of that imbalance we do not at present know, but in view of the close association of this condition with psychic disturbance, we may speculate that it is in some way related to that. The most feasible explanation would be in the nature of inhibitory impulses arising from the cortex and suppressing the sympathetic centers of the hypothalamus as well

as the neuro-endocrine pathways. Such a mechanism could give rise to the clinical and physiologic findings characteristic of neurasthenia.

Finally, one is inevitably led to the question, Are the psychic fatigue and the other psychologic stigmata of this condition the result of a constitutional vagotonia and panendocrine deficiency, or, contrariwise, are these latter the end products of specific psychosomatic mechanisms? Tintera, as noted previously, speaks for the first point of view. Our own opinion is that this attitude is limited and sterile. We feel, rather, that both mechanisms are true—that constitutional tendencies do tend to determine personality development, but that, in turn, psychologic conflicts result in physiologic changes. Where these circular processes reinforce each other, extremes of psychologic and physiologic reaction patterns result which can be delineated through careful psychologic and physiologic studies.

Summary

1. Nineteen patients with psychic fatigue were studied for evidence of autonomic nervous system and endocrine dysfunction.

2. The majority of patients showed definite evidence of fairly marked vagotonia.

3. The majority of patients also gave evidence of a panendocrine hypofunction, probably secondary to underactivity of the anterior pituitary gland.

4. The hypothesis was presented that the physiologic defect in psychic fatigue lies in the area of the hypothalamus.

Acknowledgment

The authors wish to express their gratitude to Carol B. Gallop for her technical assistance.

Summario in Interlingua

Le autores describe un characteristic profilo physiologic de fatiga psychic, consistente de augmentos de vagotonia e hypofunction panendocrin. Dece-nove patientes con marcate fatiga psychogenic esseva subjicite a un extense batteria de examines del autonome systema nervose e del systema endocrin. Iste examines habeva le objectivo de determinar le activitates relative del sympathic e parasympathic systemas nervose e del plus importante glandulas endocrin.

Le activitate del autonome systema nervose esseva analysate per medio de tres tests: (1) Le test de toleration de glucosa intravenose post quatro horas, (2) le test del reaction pressorial a frigido, e (3) le test del reflexos cardiorespiratori. Le curva del toleration pro glucosa intravenose exhibiva un anormalmente rapide degeneration in 69% de iste patientes, corroborante assi le constatationes de Alexander e Portis. Le reaction pressorial a frigido remaneva infra le limites inferior del norma in 50% del patientes, indicante assi hypoactivitate del sympathic systema nervose. Le reflexo cardiorespiratori revelava un abrupte deceleration del pulso in 53% del patientes, indicante de novo un augmento del vagotonia. In omne casos del serie, le tests indicava augmento de activitate parasympathic e reduction de activitate sympathic.

Le systema endocrin esseva examinate per medio de tests del activitate del glandula pituitari e del principal glandulas intra le sphera del tropismo pituitari—i.e. (1) le glandula thyroide, (2) le cortice adrenal, e (3) le gonades. Le function del glandula pituitari esseva evalutate indirectemente per le determination del function de glandulas intra su tropismo. Le glandula thyroide esseva testate per medio de determinationes de (a) metabolismo basal, (b) iodo ligate a proteina, e (c) cholesterol del sero. Sexanta-cinque pro cento del patientes habeva valores del metabolismo basal infra 10%; in 59% del patientes le valores del iodo ligate a proteina indicava hypothyroidismo; sed pro omne patientes le valores obtenite pro cholesterol seral esseva normal. Le association de basse valores del metabolismo basal e de basse valores de iodo ligate a proteina con normal valores de cholesterol es un characteristica de hypothyroidismo secundari a hypoactivitate del glandula pituitari anterior. Assi le hypoactivitate del glandula thyroide pote servir como indication indirecte del pituitario anterior.

Similemente, le examine del activitate del cortice adrenal e del gonades revelava combinationes de hypoactivitate pro que le pituitario esseva responsabile. Le tests usate in le studio del function del cortice adrenal esseva (1) numeration eosinophilic post ACTH, (2) numeration eosinophilic post adrenalina, (3) mesuration de 17-cetosteroides urinari, e (4) mesuration de 17-hydroxycorticoides urinari. Le prime de iste tests esseva normal in 95% del patientes, sed le secunde, le tertie, e le quarte monstrava definite signos de hypoactivitate in 50, 46, e 67 pro cento del casos, respectivemente. Le association de un normal responsa eosinophilic a ACTH con basse nivellos del eosinophilos post adrenalina, del 17-cetosteroides, e del 17-hydroxycorticoides representa etiam un indication de hypoactivitate del cortice adrenal secundari a hypoactivitate del pituitario anterior.

Le evalutation del function gonadal in feminas esseva facite per tests de (1) estrina e (2) gonadotrophina in le urina. Le distribution normal es estrina positive e gonadotrophina negative. Sexanta-tres pro cento del feminas examinate habeva estrina negative e gonadotrophina negative. Iste distribution es characteristic de hypogonadismo secundari a hypofunction del pituitario anterior.

Assi le responsas physiologic del glandulas intra le tropismo pituitari revelava in omne casos hypofunction secundari a hypoactivitate del glandula pituitari anterior. Iste effectos, combinate con le previemente describite tests del systema autonome, constitue le profilo general de marcate grados de vagotonia in association con generalisate hypoactivitate endocrin secundari a hypofunction del pituitario anterior.

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A STUDY OF MYOCARDIAL INFARCTION IN WOMEN *

By Herbert L. Weinreb, M.D., *Brooklyn, N. Y.*, Elaine German, M.D., *New York, N. Y.*, and Benjamin Rosenberg, M.D., F.A.C.P., *Brooklyn, N. Y.*

It is well known that myocardial infarction occurs much more commonly in men than in women. Almost all reports on coronary artery disease in the female emphasize a history of diabetes or hypertension as important predisposing factors. Levy and Boas,[1] in their series of 169 women with coronary artery disease, found only 7.7% to have neither disease, and "the diagnosis of coronary artery disease is open to doubt in many of these." Master et al.[2] found only 11.7% of women with infarcts to have neither diabetes nor hypertension.

Because in the authors' experience the diagnosis of coronary thrombosis has not infrequently been overlooked in women with normal blood pressures and no diabetes, the following study was undertaken to reassess some of the factors that might be important in predisposing to myocardial infarction in women.

Methods and Materials

The records of admissions during the years 1945–55 to the Maimonides Hospital of Brooklyn, a large voluntary general hospital, were reviewed. All charts carrying a final diagnosis of arteriosclerotic heart disease were examined in detail. Cases were selected on the basis of unequivocal electrocardiographic evidence of myocardial infarction (criteria of the New York Heart Association), or, in a few instances, of autopsy findings of coronary occlusion with myocardial necrosis. Follow-ups were obtained by questionnaires completed by the patients' private physicians and often by personal communication with the patients and their families.

Data were obtained as to the following:

1. Age at admission
2. Age at time of myocardial infarction
3. Age at onset of angina
4. Presence of diabetes
5. Presence of hypertension
6. Level of serum cholesterol
7. Family history
8. Menstrual history
9. Mortality and follow-up

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Requests for reprints should be addressed to Benjamin Rosenberg, M.D., Department of Medical Services, Maimonides Hospital of Brooklyn, 4802 Tenth Avenue, Brooklyn 19, N. Y.

TABLE 1

Age Distribution, by Decades, of 231 Women at the Time of Their First Myocardial Infarction

Age	Number	Per Cent
30–39	5	2.3
40–49	24	11.0
50–59	54	24.6
60–69	103	47.1
70–79	29	13.2
80 and over	4	1.8
	219	100.0
Age unknown	12	
Total	231	

Information concerning dietary habits and body build was unfortunately not available to us.

A total of 231 cases of proved myocardial infarction in women form the basis of this report. Among these, a subgroup of 29 women who suffered their first infarct before 50 years of age is compared with the remaining patients.

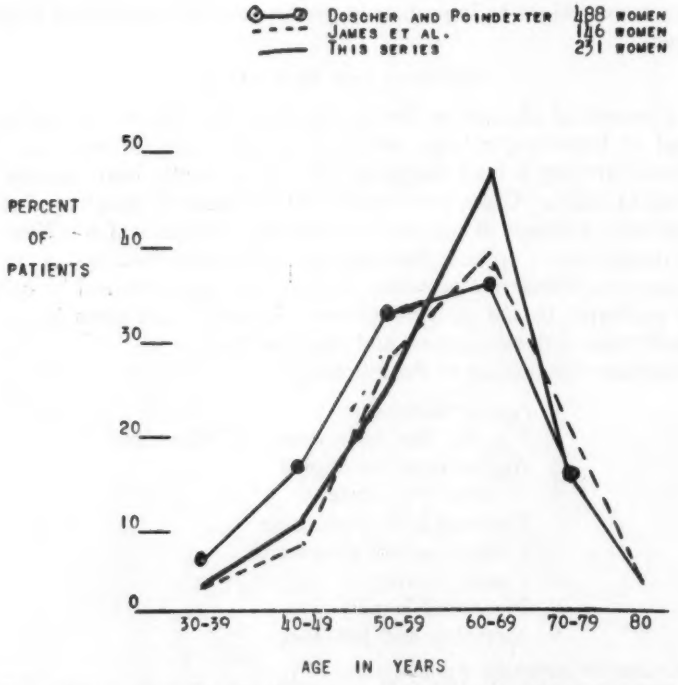


FIG. 1. The age distribution of women with myocardial infarction reported in three large series.

Results

Age: The age distribution of the patients at the time of their first myocardial infarction is presented in table 1. The average age at the time of the first infarct was 61.9 years. James, Post and Smith [3] report an average age of 64 years in their study of coronary disease in women. The distribution of ages in our series is similar to theirs and to that of 488 cases collected from the literature by Doscher and Poindexter.[4] Our age curve shows a somewhat sharper peak as the incidence of infarction reaches a maximum in the 60–69 year age group (figure 1).

Hypertension: Reliable records of systolic and diastolic blood pressures *prior* to their first myocardial infarction were obtained in 169 patients (73%). In addition, 51 patients (22%) gave a history of hypertension, though accurate figures were not available. In 11 cases no information was obtainable concerning blood pressures prior to infarction.

In the absence of entirely satisfactory criteria for arterial hypertension, blood pressures were divided into three groups, as follows:

	No. of Patients	Per Cent
Group A—BP less than 140/90 (normotensive)	50	29.6
Group B—Both systolic and diastolic BP greater than 140/90 (diastolic hypertension)	87	51.5
Group C—Systolic blood pressure greater than 140; diastolic pressure 90 or less (systolic hypertension)	32	18.9
Total	169	100.0
Group B was further subdivided as follows:		
B1—diastolic BP 91–100	36	41.4
B2— 101–110	33	38.0
B3— 111–120	11	12.6
B4— over 120	7	8.0

According to our criteria, then, 51.5% of these women had an elevated diastolic pressure, a condition that we feel represents significant hypertension. The incidence of hypertension in women with myocardial infarction, as reported in six large series totaling 833 women,[5, 6, 2, 7, 4, 3] varies from 48.6% to 80%. The discrepancies appear to lie chiefly in the selection of criteria for hypertension. However, Doscher and Poindexter,[4] using a diastolic pressure of more than 100 mm. Hg, Mintz and Katz,[6] with a maximal normal pressure of 140/90, and James's group,[3] with upper limit of normal at 160/100, report incidences very close to ours. Sigler,[5] using 140/90 as maximal normal, finds that 79.4% of his women with coronary artery disease have hypertension.

Table 2 shows the distribution of blood pressures in our series by age group in decades. The incidence of diastolic hypertension remains about the same with increasing age, while the incidence of systolic hypertension

rises chiefly at the expense of the normotensive group. In the women under 50 years of age, systolic hypertension was absent. The incidence of diastolic hypertension was 55%, approximately the same as that found in the group as a whole.

Cholesterol: All cholesterols were determined by the Bloor method (normal, 130 to 280 mg.%). Determinations made at variable intervals before or after the acute attack were available in 158 patients (68.6%). The results are tabulated in table 3.

TABLE 2

Distribution of Blood Pressure Groups A, B and C Among the Patients by Age Groups in Decades

Age	Number	Per Cent Group A (Normotensive)	Per Cent Group B (Diastolic Hypertension)	Per Cent Group C (Systolic Hypertension)
30–39	5	60.0	40.0	0.0
40–49	20	40.0	60.0	0.0
50–59	43	34.9	53.5	11.6
60–69	68	23.5	53.0	23.5
70–79	22	31.8	36.4	31.8
80 and over	1	0.0	100.0	0.0

The mean cholesterol level was 258 mg.%; the incidence of hypercholesterolemia was 44.3%. Morrison and co-workers [8] found cholesterol levels in excess of 260 mg.% in 45.5% of 200 patients of both sexes with coronary occlusion, while 97% of 30 normal persons had serum cholesterol levels below this figure. Katz et al.[9] noted similar mean total cholesterols in normal women and in women with coronary artery disease, while finding higher Sf 12–20 lipoprotein levels in the latter.

TABLE 3

Distribution of Serum Cholesterol Levels in 158 Women with Myocardial Infarction

Cholesterol Level (mg.%)	Number of Patients	Per Cent
Less than 130	1	0.6
130–280	87	55.1
280–350	51	32.3
Over 350	19	12.0
	158	100.0

In the subgroup of patients under 50 years of age, the distribution of cholesterol levels was very similar to that shown in table 3; the incidence of hypercholesterolemia was 39.1%. However, since cholesterol levels rise with age, particularly in women, the incidence of hypercholesterolemia adjusted for age would no doubt be higher in this younger group.

Diabetes: The difficulties one may encounter in establishing a diagnosis of diabetes without a properly performed glucose tolerance test are well

TABLE 4

Diabetic Status of 215 Women with Myocardial Infarction

	Number of Patients	Per Cent
Group I (Definite Diabetes)	113	52.6
Group II (Equivocal Diabetes)	28	13.0
Group III (No Diabetes)	74	34.4
	215	100.0

Criteria employed to assign a patient to one or another group are as follows:

Group I—FBS over 120 mg.% or GTT with blood sugar over 120 mg.% at two hours.
Group II—FBS 100–120 mg.% or GTT with blood sugar 100–120 mg.% at two hours.
Group III—FBS less than 100 mg.% or normal GTT.

(Normal FBS in our laboratory is 60–100 mg.%—modified Somogyi method.)

known. The situation is aggravated in acute coronary thrombosis. Several authors have noted diminished glucose tolerance during the acute phase of myocardial infarction.[11, 12]

Information concerning the presence of diabetes was available in 215 patients (93%). Of these, 104 patients had had two or more fasting blood sugar determinations and 20 had had glucose tolerance tests performed while in the hospital.

Most series reported in the literature do not give their criteria for making the diagnosis of diabetes mellitus. We have arbitrarily divided our patients into the groups shown in table 4.

It is seen that 52.6% of our patients had definite diabetes. Of 327 women with infarcts reported in the literature, 30.9% had diabetes.[4] In the series of James et al.,[3] 21.2% of 146 female patients with coronary artery disease had diabetes.

In the subgroup of women under 50 years, the incidence of diabetes is almost the same as in the series as a whole. The number of patients in Groups 1, 2 and 3 is 13 (44.9%), and Smith [13] found only one case of diabetes among 27 women under the age of 40 with coronary artery disease.

Master and associates [2] state that the incidence of diabetes among women

TABLE 5

Incidence of Diabetes in Women with Myocardial Infarction by Age Group in Decades. Comparison of Our Data with Those of Master and Associates[2]

Age Group	Master: 112 Patients, Incidence of Diabetes (Per Cent)	Total Patients in Our Group	Diabetes	
			No.	Per Cent
30–39	—	5	1	20.0
40–49	4.5	24	12	50.0
50–59	20–25	54	20	37.1
60–69	35–40	103	52	50.5
70–79	50	29	17	58.7
80 and over	—	4	2	50.0
Total	26	219	104	48.4

with myocardial infarction rises with age. As table 5 demonstrates, the women over 40 years of age in our series all show an incidence of diabetes close to 50% except for those in the 50–59 year decade, where the frequency is somewhat lower.

Angina: Among our patients, 46.7% had anginal pain which began at least one month prior to the first myocardial infarction. The average age of onset was 58.5 years, or 3.4 years before the first infarct. This is similar to the prevalence of angina preceding infarction previously reported.[4] Angina was more frequent in the 29 women under 50 years (65.5%). Three patients who had their first infarct following the menopause had had angina four, nine and 18 years prior to the cessation of the menses. James et al.[3] found that none of their patients who had the initial infarction after the menopause had had angina before it.

TABLE 6

Location of 237 Myocardial Infarctions in Women

Location	Acute No.	Infarcts Per Cent	Old Infarcts		Total Infarcts	
			No.	Per Cent	No.	Per Cent
Anterior	30	17.5	7	10.6	37	15.6
Anteroseptal	52	30.4	18	27.3	70	29.6
Anterolateral	8	4.7	1	1.5	9	3.8
High lateral	1	0.6	2	3.0	3	1.2
Posterior	56	32.8	34	51.5	90	38.0
Posteroseptal	4	2.3	1	1.5	5	2.1
Posterolateral	8	4.7	2	3.0	10	4.2
Through-and-through septal	5	2.9	1	1.5	6	2.5
Anterior and posterior	7	4.1	0	0.0	7	3.0
	171	100.0	66	100.0	237	100.0
Total anterior	90	52.6	26	39.4	116	49.0
Total posterior	68	39.8	37	56.0	105	44.3

Location of Infarct: Electrocardiograms were obtained in all but one patient. In 159 cases (68.9%), recent myocardial infarction was diagnosed; in 54 (23.4%), the tracing revealed an old infarct; in 12 (5.2%), both old and recent infarcts were noted. The remaining five tracings were interpreted as: normal; LBBB; clockwise rotation; and myocardial ischemia (twice). In these five cases, as in the patient with no electrocardiogram, the diagnosis of infarction was made at autopsy. The location of the 237 infarcts is described in table 6.

The findings are in substantial agreement with those of Doscher and Poindexter [4] and Mintz and Katz,[6] but not with Baker and Willius,[7] who found that among 86 patients, 30 had anterior and 50 posterior wall infarcts.

In the subgroup of women under 50 years, 48.4% had anterior and 37.9% had posterior wall infarction. Two patients had had a previous infarct.

Family History: Information as to the presence or absence of hypertension, diabetes and coronary artery disease in members of the immediate families (parents, children, siblings) was obtained in 136 patients (58.9%). Table 7 lists the information obtained.

Sixty-eight and four tenths per cent of the patients gave a positive family history for at least one factor. In the younger group, all but three of the 22 patients in whom information was available had a positive family history, an incidence of 86.4%.

It is of interest that Thomas and Cohen, in their study of the familial occurrence of hypertension and coronary artery disease, found that both diseases were much more prevalent among siblings of individuals with these maladies. They also noted that diabetes was eight times as prevalent among siblings of diabetic persons as among siblings of nondiabetics.[14]

TABLE 7

Family History in 136 Women with Myocardial Infarction

History	Per Cent
History negative	31.6
Hypertension	35.3
Diabetes	40.5
Coronary artery disease	30.9
Hypertension only	11.0
Diabetes only	20.6
Coronary artery disease only	5.9
Hypertension and diabetes	5.9
Hypertension and coronary artery disease	11.0
Diabetes and coronary artery disease	6.6
Any two	23.5
All three	7.4

Menopause: Considerable attention has recently been focused upon the possible rôle of estrogens in protecting against arteriosclerosis. We have attempted to relate the age of the patients at the time of their first infarct with available data concerning the menopause to see if any information relevant to this theory could be obtained.

Satisfactory histories were given by 168 patients (72.7%). Of these, 15 (9%) were still menstruating at the time of their first infarct; 122 (72.6%) had had a natural menopause; 11 (6.5%) had had bilateral oophorectomies, and 18 (10.7%) had had hysterectomies. The average age at natural menopause was 47.5 years, which is almost identical with that quoted for women as a whole.[15, 16] The average interval between natural menopause and first infarct was therefore 14.4 years. In the small group of oophorectomized patients, the average age at castration was 42.7 years, and of initial infarction, 59.5 years, an interval of 16.8 years. The difference between intervals is not statistically significant. The groups are of course small, and there was tremendous individual variation in intervals in both groups (— 3 to 30 years in the women with natural menopause, and three to 34 years in the oophorectomized group). In addition, the average

age at operation preceded the expected occurrence of natural menopause by only a few years in most cases.

Follow-up and Mortality: Follow-up data were available in 166 cases (71.5%). Of these, 51 died while in the hospital. Information concerning the other patients was obtained from their private physicians in 38 cases, by communication with the patients and their relatives in 43 instances, and in both ways in 32 cases. The data obtained are shown in table 8.

A total of 86 patients died (58.5%); 45 of these died with the acute attack, and 15 died of a subsequent coronary occlusion two months to 10 years later. In the remainder, death was due to unrelated or unknown cause. The percentage of deaths with the first acute infarct increased with age, a finding previously reported.[4] Only two patients survived more than 10 years; one of these is now dead.

TABLE 8

Follow-ups in 166 Women with Myocardial Infarction

	Total Group		Women Less than 50 Years of Age	
	No.	Per Cent	No.	Per Cent
Patients dead with first acute infarct	45	27.2	3	13.6
Patients dead 2 to 12 months later	9	5.4	0	0.0
Patients dead 1 to 5 years later	21	12.6	1	4.6
Patients dead 5 to 10 years later	10	6.0	2	9.1
Patients dead more than 10 years later	1	0.6	1	4.6
Total dead	86	51.8	7	31.9
Patients now living up to one year after infarct	10	6.0	2	9.1
Patients alive 1 to 5 years later	62	37.4	9	40.9
Patients alive 5 to 10 years later	7	4.2	4	18.1
Patients alive more than 10 years later	1	0.6	0	0.0
Total patients now living	80	48.2	15	68.1

Of the 80 patients still living, 70 have been followed more than one year after infarction. At present 30 have angina, 12 are in varying degrees of congestive failure, six have suffered and survived another myocardial infarct, and 31 are asymptomatic with regard to arteriosclerotic heart disease as far as can be determined.

In the subgroup of younger women, follow-up data were obtained in 22 cases. Of these, seven have died, three with the acute episode. Thirteen patients have survived at least one year after infarction, and of these, four are alive more than five years later.

Table 9 presents the mortalities at two months, one year and five years following myocardial infarction in our patients according to blood pressure, presence of diabetes, cholesterol level, presence of angina, and location of infarct.

It is seen that hypertension appears to play no rôle in prognosis. Doscher and Poindexter [4] found a higher mortality in female patients with myocardial infarction whose blood pressures were elevated. However, others have noted no difference in prognosis between hypertensives and normotensives.[2, 6]

The immediate mortality was twice as high among diabetics as among nondiabetics—38% compared with 19%. A marked difference is also noted in deaths a year after infarction and, to a lesser degree, at five years. These findings agree well with those of Master's group [2] and with Mintz and Katz,[6] but Doscher and Poindexter [4] found no increased mortality among diabetics with myocardial infarction.

TABLE 9

Cumulative Mortality Following Myocardial Infarction in Certain Patient Subgroups

	At Two Months		At One Year		At Five Years	
	Number Followed	Per Cent Dead	Number Followed	Per Cent Dead	Number Followed	Per Cent Dead
Diastolic hypertension	64	28	61	34	35	80
Normotension	40	25	36	33	16	80
Systolic hypertension	19	32	18	39	9	78
Diabetes	82	38	77	48	51	88
No diabetes	54	19	50	20	24	71
High cholesterol	54	22	51	24	25	76
Normal cholesterol	55	29	50	44	32	94
Angina present	71	27	67	36	40	85
Angina absent	90	33	84	40	51	82
Total anterior wall	73	25	68	35	51	61
Total posterior wall	64	36	60	45	39	87
Acute anterior wall	60	28	60	35	30	90
Acute posterior wall	43	47	41	56	27	100
All patients	166	27	156	35	94	79

A somewhat better prognosis for patients with high cholesterol levels at one and five years after infarction is indicated by our data. The reason for this is not clear. It would seem to conflict with the report that the recurrence rate of myocardial infarction is greater in patients with Sf 12–20 lipoprotein levels.[23]

There is no significant difference in mortality between patients with preceding angina and those without this symptom. Levine and Rosenbaum [18] reported similar findings, while Doscher and Poindexter [4] noted a poorer prognosis in patients with angina.

Our data indicate that acute posterior wall infarction is associated with a worse prognosis than is anterior wall infarction. This difference is much less marked when both acute and old infarcts are considered. Other investigators [17, 18] report no significant difference in mortality between these groups. Though no specific studies of the incidence of arrhythmias in

patients with the two infarct locations were made, the known higher occurrence of this complication in posterior infarction may explain this finding.

Discussion

Appreciation of the clinical features of myocardial infarction in women has lagged due to its lesser incidence in the female sex. Many clinicians are still prone to suspect disease of the gall-bladder and gastrointestinal tract rather than the coronary arteries in women complaining of chest pain, especially if the patients are young and if they have no evidence of diabetes or elevated blood pressure.

The presence of cholesterol in atherosclerotic lesions has stimulated speculation and experimentation designed to elucidate the relationship between lipid metabolism and atherosclerosis. Many studies have attempted to correlate lipid fractions of the serum with clinical manifestations of atherosclerosis or with findings at autopsy.

Serum cholesterol levels in normal people vary somewhat from time to time. This tendency is more marked in patients with myocardial infarction.[19, 20] Nevertheless, significantly higher mean total cholesterol levels have been reported in patients with coronary artery disease compared with a control group.[8, 20] A closer correlation is said to exist between atherosclerosis and Sf 12–20 lipoprotein molecules than with cholesterol, and higher levels of these lipoproteins have been reported in the serum of women with coronary artery disease than in the serum of normal women.[21, 22, 9, 23] Katz et al. have warned, however, that a wide range of normals is seen, and that care must be taken in interpretation.[9] Recently, Paterson and associates have formed the opinion that elevations in Sf 12–20 molecules bear no relationship to the amount of atherosclerosis found at autopsy if the serum cholesterol levels are below 300 mg.%.[24]

Almost half our patients had cholesterol levels above 280 mg.%. There were no marked differences in the incidence of hypertension or diabetes among these patients compared with those who had normal levels.

The significance of hypertension as a condition predisposing to coronary artery disease is uncertain. Indeed, the very meaning of an elevated blood pressure as a pathologic entity has been questioned.[25] Several studies have indicated that blood pressure rises gradually with age, that pressures in excess of 140/90 mm. Hg are common in relatively asymptomatic women in the older age groups, and that there is no sharp dividing line between normotension and hypertension.[26, 27] Nevertheless, in this study we have taken blood pressures in excess of 140/90 mm. Hg to indicate hypertension. This was done in recognition of the observation that subjects with pressures below this level show no significant rise of blood pressure with age and have a longer life span.[28]

Our study reveals a high incidence of diastolic hypertension in women with myocardial infarction at every age level. The incidence in women

under 50 years (55.0%) is about the same as in those over 50 (51.0%). In every decade except the eighth, the frequency of hypertension in our patients is greater than in a large group of female clinic patients [26] (table 10).

It can be seen from the table that the tendency to antecedent hypertension is particularly significant in the younger women who develop myocardial infarction; in the older age groups, the incidence of hypertension is not significantly different from that in a general clinic population.

Sigler,[5] despite an unusually high prevalence of hypertension in his patients with coronary occlusion, felt that there was no direct etiologic relationship. Thomas and Cohen note that, in their series, hypertensive people have more coronary artery disease than normotensive people, and that the familial frequency of occurrence of the two illnesses together is significantly greater than could be ascribed to chance.[14]

TABLE 10

Incidence of Diastolic Blood Pressures Greater than 90 mm. Hg According to Age Groups. Comparison of the Women in This Series to Patients in a General Clinic Population[26]

Age Group	Our Patients		Hamilton et al.	
	Number	Per Cent	Number	Per Cent
30–39	3	33.3	227	7.9
40–49	17	58.8	236	12.7
50–59	44	54.5	239	29.3
60–69	69	53.6	161	43.8
70–79	34	38.2	86	46.5
80 and over	2	100.0	—	—

The higher incidence of diabetes among our patients (52.5%) compared with other reports may be due in part to the fact that the majority of the patients admitted to the Maimonides Hospital are of Jewish descent (89.7% in the present series). In addition, evidence for diabetes was usually sought for carefully, with multiple fasting blood sugar determinations and glucose tolerance tests in doubtful cases.

At all ages, the incidence of diabetes in this series is many times that in the general female population,[34] the greater discrepancies appearing in the youngest age groups. With the easy availability of insulin and familiarity with its use, the major "complications" of diabetes today are vascular. The average degree of sclerosis of the coronary arteries is higher in every decade in diabetics compared with nondiabetics, except in the ninth decade.[29] Root and colleagues note a much greater frequency of coronary occlusion in diabetics than in normals at every age.[35]

Diabetes may be implicated in coronary artery disease by virtue of the associated alteration in lipid metabolism. Elevated serum Sf 12–20 lipoprotein levels are reported in diabetic women,[21, 9] though Collens, Banowitch and Colsky find this to be true only in the presence of diabetic nephropathy.[36] There is no significant difference in mean total cholesterol levels between

diabetic and nondiabetic women.[9] This is confirmed in the present study, a finding in agreement with Liebow's,[37] who found no correlation between cholesterol levels and coronary artery disease in diabetics.

Does diabetes predispose to atherosclerosis because of an increased association with hypertension? Waite and Beetham found diastolic pressures higher than 90 mm. Hg in 23.2% of 2,002 diabetics.[38] The incidence in a general clinic population, however, is similar—20.8%.[25] Others have noted more hypertension (usually defined, however, as to include systolic hypertension) among diabetics than among nondiabetics.[39-41] Liebow et al. concluded that hypertension was an important condition predisposing to arteriosclerotic heart disease in the presence of diabetes.[37] In our series we note a tendency, though not marked, to an increased association between diabetes and hypertension in women with coronary occlusion; diastolic pressures over 90 mm. Hg were recorded in 54.5% of the diabetics and in 42.1% of the nondiabetics.

Our data would indicate that diabetes mellitus plays a major rôle in the pathogenesis of coronary artery disease in women. As indicated above, the mechanisms are not completely understood. Lipid changes and hypertension do not seem to account fully for the relationship between diabetes and myocardial infarction.

In our series, 156 patients had accurate information relating to the presence of hypertension and diabetes. Of these, 13.5% had normal blood pressures and no diabetes. The age distribution in this group was 11.3% among the 133 women over age 50, and 26.1% among the 23 patients under 50.

Of the 15 women over 50 who had neither disease, 10 had hypercholesterolemia, and in two instances cholesterol determinations were not done. Only three patients had normal cholesterol levels, and all three had a positive family history of hypertension, diabetes or coronary artery disease.

In comparison, only one of the six women under 50 with neither disease had hypercholesterolemia, and one patient's level was unknown. Four women had normal levels. Of these, two had positive family histories and two did not.

Thus, of the entire group of women with myocardial infarction about whom sufficient information was obtained, only two had no evident factor predisposing to myocardial infarction.

One may well ask why myocardial infarction occurs more commonly among men than women. Dock found a thicker coronary artery intima among male infants, and suggested that men are more susceptible to atherosclerotic disease from birth.[42] Others have found that in the younger age groups, women have less Sf 12–20 lipoprotein in their serum than do men.[20]

Recently, attention has been focused upon the female sex hormones as possible protective factors against coronary artery disease. Wuest and associates noted more severe atherosclerosis in the hearts of 61% of 49

bilaterally oophorectomized women than in the hearts of normal women of the same ages (though there was less than in normal men).[43] There was no significant increase in intimal change until five years had elapsed after operation. Only 6% of such women, however, had clinical evidence of coronary artery disease. Experiences in treating patients with estrogens and observing serum lipid changes have been reported. Glass [44] found no significant changes; Steiner et al.[45] and Eilert [46] noted a fall in the cholesterol-phospholipid ratio in the treated patients. Boyle [47] and Barr et al.[48] report a rise in the alpha-to-beta lipoprotein ratio, i.e., the pattern after treatment more nearly resembled that seen in normal women. Stamler and colleagues [49] presented suggestive evidence of a reduced recurrence rate among men who had sustained a previous infarct and were treated with estrogens compared to a placebo-treated group. In autopsy material, Rivin and Dimitroff [50] found decreased atherosclerosis in men with prostatic carcinoma treated with large doses of estrogens. Women who had undergone castration had a greater degree of atherosclerosis than did controls, while women with carcinoma of the breast (considered to be hyperestrogenic) had less.

We were unable to demonstrate a significant difference in time interval before infarct or onset of angina between a small series of oophorectomized women with infarction and a larger group with a history of natural menopause. However, individual variations were very great and the number of patients few. More extensive clinical studies of myocardial infarction in oophorectomized women would be of great interest.

Summary and Conclusions

1. A series of 231 women with proved myocardial infarction is presented and the major clinical features are described.

2. The group as a whole shows an increased frequency of diastolic hypertension (51.5%), diabetes mellitus (52.6%), and elevated serum cholesterol (44.3%).

3. A positive family history of diabetes, hypertension or coronary artery disease was present in more than two thirds of the patients.

4. A strikingly poorer prognosis was noted among the women with diabetes than among the nondiabetics.

5. Of 156 patients about whom information was available, 13.5% had neither diabetes nor hypertension. Of the 23 women in this group under the age of 50 years, 26.1% had neither disease.

6. Only two women, both under 50 years at the time of their first myocardial infarct, did not have diabetes, hypertension, hypercholesteremia or a positive family history.

7. Coronary artery disease must be seriously considered in women presenting a suggestive clinical picture, particularly in the younger age group, despite the absence of hypertension or diabetes mellitus.

SUMMARIO IN INTERLINGUA

Esseva studiate un gruppo de 231 feminas con verificate infarcimento myocardial. Illas esseva patientes in un grande hospital general voluntari. Vinti-nove de iste feminas forma un sub-gruppo in tanto que illas experientiava lor prime infarcto myocardial ante le etate de 50 annos. Le casos del sub-gruppo es comparate con le casos del remanente patientes in le gruppo total. Le distribution del etates del patientes al tempore de lor prime infarcto esseva simile a illo reportate super le base de altere grande series. Le etate medie amontava a 61,9 annos.

Le gruppo monstrava un augmento del frequentia de hypertension diastolic (51,5%), de diabete mellite (52,6%), e de elevation del nivello seral de cholesterol (44,3%). Le incidentia de iste conditiones non differeva significativemente inter le feminas de plus juvene etates. Angina de pectore occurrente ante le infarcimento myocardial esseva plus commun in le plus juvene gruppo (65,5%) que in le gruppo total (46,7%).

Esseva constatate electrocardiographicamente que 49,0% del infarctos esseva de location anterior; 44,3% esseva posterior. Le resto esseva septal, alti-lateral, o anterior e posterior in combination.

Quasi 70% del feminas habeva positive historias familial de diabete, hypertension, o morbo de arteria coronari.

Le historias menstrual revelava que 9% del feminas menstruava ancora al tempore de lor prime infarcto; 72,6% habeva habite un menopause natural; 6,5% habeva habite oophorectomias bilateral, e 10,7% habeva habite hysterectomias. Nulle conclusiones poteva esser formulate relative al influentia de oophorectomia precoce super le occurrentia de infarcimento myocardial. Pro isto le numero del patientes non esseva satis grande.

Vinti-septe pro cento del patientes moriva per le attacco acute; 35% esseva morte al fin de un anno; 79% esseva morte al fin de cinque annos. Solmente duo patientes superviveva plus que dece annos post lor prime infarcto. Le mortalitate immediate cresceva constantemente con le etate. Illo esseva duo vices plus alte inter diabeticos que inter non-diabeticos. Le mortalitate non esseva afficite notabilemente per le pression diastolic de sanguine, per le nivellos seral de cholesterol, o per le previe occurrentia de angina. Acute infarcimento del pariete posterior esseva associate con un prognose alique pejor que infarcimento del pariete anterior.

Le datos in iste serie pare indicar que diabete mellite es particularmente importante como factor predisponente in le occurrentia de infarcimento myocardial in feminas. Hypertension e elevate nivellos seral de cholesterol ha apparentemente un rolo minus significative. In le opinion del autor, le alterationes lipidic e le tendentia hypertensive que es notate in le diabeticos non explica completemente le relation inter diabete e infarcimento myocardial.

Solmente duo feminas habeva ni diabete, ni hypertension, ni hypercholesterolemia, ni positive historias familial. Ambes habeva etates de minus que 50 annos al tempore de lor prime infarcto. Del altere latere, 13,5% del feminas del gruppo total habeva ni diabete, ni hypertension, durante que le incidentia correspondente in feminas infra 50 annos amontava a 26,1%. Iste facto pare indicar que morbo de arteria coronari debe esser considerate como un diagnose possibile in feminas qui se presenta con suspecte symptomas clinic, mesmo si diabete e hypertension es absente. Isto vale specialmente pro le gruppo de etates plus juvene.

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PITUITARY TUMORS *

By CARL W. RAND, M.D., and ROBERT W. RAND, M.D., Ph.D.,
Los Angeles, California

A careful review of records of pituitary tumors impresses one with the variety of symptoms they may produce. We have 100 such records of patients observed in private practice and wish to review them briefly and consider some experiences of others. Of these cases, 65 were males whose ages varied from 10 to 80 years; 35 were females whose ages varied from 14 to 64 years. They fall into the following categories: 37 verified solid chromophobes, 10 verified cystic chromophobes, 28 unverified chromophobes, 14 unverified chromophiles, nine primary malignancies and two metastatic tumors.

Sixty-five per cent of these patients came to us complaining of failing vision alone, and 11% more because of failing vision and headache. Therefore 76% of the patients had failing vision as at least one of their presenting symptoms. The shortest duration of this symptom was two weeks; the longest had existed for 10 years. Eventually 83% of patients developed visual disturbances, indicating involvement by tumor of the optic nerves, optic chiasm or optic tracts. We noted the longest period of visual disturbance in patients with chromophobe tumors. In the instance of an 80 year old man, the duration of failing vision could not be accurately determined because of cataracts. Only after these had been removed was a bitemporal hemianopsia discovered. Skull x-rays revealed a marked enlargement of the sella turcica. His visual symptoms markedly improved after irradiation. One patient who was completely blind with loss of light reflex in both eyes regained, by operation, useful vision which lasted for six years. Two other patients were completely blind in one eye for several days prior to surgery. Useful vision was recovered in each instance.

Loss of vision due to pituitary tumors usually follows a characteristic pattern. Progressive loss appears first in the upper temporal quadrants, to be followed by similar loss in the lower temporal quadrants. The lower nasal quadrants are next affected, until finally only an island of peripheral vision is left in the upper nasal areas. However, visual loss need not be symmetric if the growing tumor does not press equally on the optic nerves or the chiasm. The vision in one eye alone may be affected, or a homonymous hemianopsia may even develop, depending upon the unequal pressure resulting from the character and rate of growth of the tumor.

The presenting symptom of headache in 19% of the patients usually was described as being frontal or bitemporal in character. It was most severe

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Requests for reprints should be addressed to Carl W. Rand, M.D., 2010 Wilshire Boulevard, Los Angeles 57, California.

in the acromegalic patients, and often seemed quite out of proportion to the degree of enlargement of the sella and the visual symptoms. Some believe the pain is related to bony changes taking place in the skull or face. Once we noted at surgery in a patient with severe acromegalic headache that the tumor did not even press on the chiasm or optic nerves. On the other hand, Henderson [12] observed that adenomas have been known to surround the optic chiasm and nerves without causing visual disturbances. Several acromegalic patients with severe headaches had normal visual fields. Unfortunately, these severe headaches have thus far been refractory to surgical or medical management. They are similar to those of patients suffering from Paget's disease of the skull.

Patients who harbor chromophobe adenomas generally develop a rather characteristic appearance, described as the hypopituitary habitus or state. It may be mild or severe, depending upon the degree of compression and destruction of the remaining functioning hypophysis. The skin is thin, dry and depigmented, giving it a sallow cast; secondary sexual characteristics undergo retrograde changes, with loss of pubic and axillary hair. The beard becomes thin. The fingers become tapered and the nail moons, except for the thumb, are lost. Young women may become amenorrheic, and men may show testicular atrophy and exhibit loss of sexual power. Ease of fatigue and sensitivity to cold increase as hypoadrenalism and hypothyroidism develop.

Four women in our series had irregular periods, two of whom were improved by irradiation of their tumors. Fifteen females (45.6%) were amenorrheic when first seen. In one only were menstrual periods resumed after operation. Some believe that removal of the adenoma, even in part, may produce amenorrhea. This did not occur in our series. The size of the tumor is not necessarily related to the duration of amenorrhea, although pressure on the hypothalamus has been reported to produce it. Younghusband et al.[24] have stated that amenorrhea without hot flashes in a young woman should arouse suspicion of a chromophobe adenoma.

It is well known that during pregnancy physiologic changes occur in the hypophysis. According to Erdheim and Strumme,[9] the average weight of the pituitary gland in nulliparae is about 0.5 gm. During the first pregnancy the weight increases to 1.0 gm. Incomplete recession of the size of the gland follows delivery, the average weight in nonpregnant women who have borne children being 0.75 gm. and slightly higher if there have been multiple pregnancies. The extreme weight following many pregnancies is 1.75 gm. An acidophile-like cell originating from the chromophobe cell during pregnancy which has been referred to as the "pregnancy cell," may account for the increased size of the gland during gestation.

Seldom does a chromophobe adenoma develop in conjunction with these changes. However, a case of the latter circumstance occurred in our series. A 32 year old housewife came to our attention in 1934 complaining of dis-

turbed vision two weeks after delivery of her second normal child. A number of months before this last pregnancy her periods had become irregular and scanty. During the seventh month of gestation she had first noticed progressive blurring of vision, decrease in temporal vision and mild headaches. The optic discs were moderately pale; however, the vessels were of good caliber. Her visual field tests showed an incomplete bitemporal hemianopsia, with acuity VOS 20/30; VOD 20/40. Deep x-ray therapy was given, following which her fields improved. Subsequent courses of irradiation were necessary two and eight years later because of recurrence of visual failure. Ten years thereafter, or 18 years after the patient was first examined, the bitemporal defects again developed. An intracapsular removal of a typical solid chromophobe adenoma was accomplished at operation. The tumor pressed upon both the optic chiasm and nerves, which appeared rather white. Her visual fields promptly improved and for the last three years have remained essentially normal. It is interesting to speculate whether her tumor, apparently stimulated by the pregnancy, developed in fact from one of the subclinical adenomas described by Loewenstein [20] and Costello [7] as being present in 25% of normal individuals, or from the so-called "pregnancy cells" described above.

Impotence in the male was partial or progressive in 10 cases; it was complete in seven. In no instance was potency restored once it had been lost. That spermatogenesis may occur in a severely hypopituitaric man incapable of consummating the sexual act was demonstrated in one of our patients, who fathered two daughters by artificial insemination.

Approximately one third of our patients were either hypotensive (7.6%) or hypertensive (26.1%). The lowest blood pressure recorded was 85/45 mm. of Hg in a 51 year old male with a huge chromophobe tumor. He finally went blind after having had symptoms for 24 years. The highest recorded blood pressure was 220/140 mm. of Hg, of 20 years' duration, in a patient who finally succumbed to cerebral hemorrhage. All of our cases with hypotension or hypertension had large tumors. This was established indirectly by visual changes, or sellar deformity as evidenced by roentgenology, or directly at the time of surgery. Thus blood pressure recordings in patients harboring pituitary tumors are of great significance, in that adrenal insufficiency is suggested by hypotension, and hypothalamic compression by hypertension. In either case the surgical risk is great.

Other than the optic nerve, the oculomotor is the most commonly affected cranial nerve. This may occur at the base of the midbrain, in the cavernous sinus or at the supraorbital fissure. Cavernous sinus syndromes, in which the oculomotor, trochlear, abducens and ophthalmic division of the trigeminal nerves are involved partially or completely in various combinations, have frequently been considered to be associated with malignant growths that have burst through their capsules. Of the four cases occurring in our series, two were caused by verified chromophobe adenomas, one of

which was questionably malignant, the third and fourth being due to unverified chromophobe and acidophilic tumors.

The following case illustrates both cavernous sinus and temporal lobe extension.

Case Report

A 33 year old white married male noted a sudden left temporal headache associated with pain in the left eye in September, 1945. Earlier in the year his appetite had increased greatly and he gained 75 pounds, reaching a weight of 250 pounds.

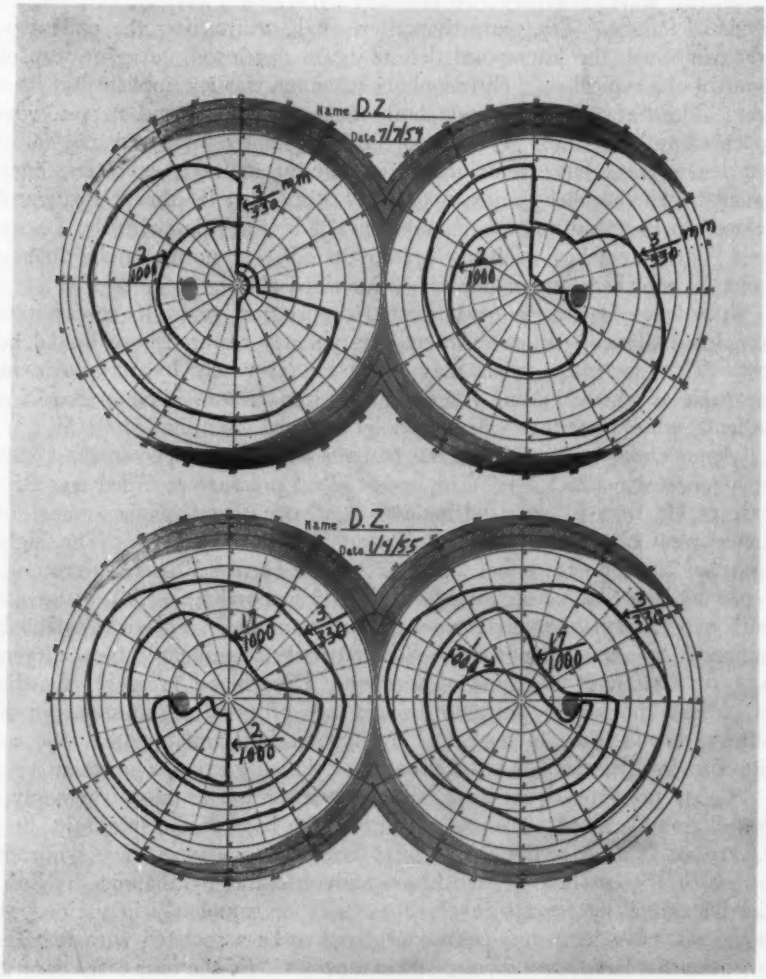


Fig. 1. Condition of perimetric fields (above) before operation; (below) six months after operation, in case of D. Z.

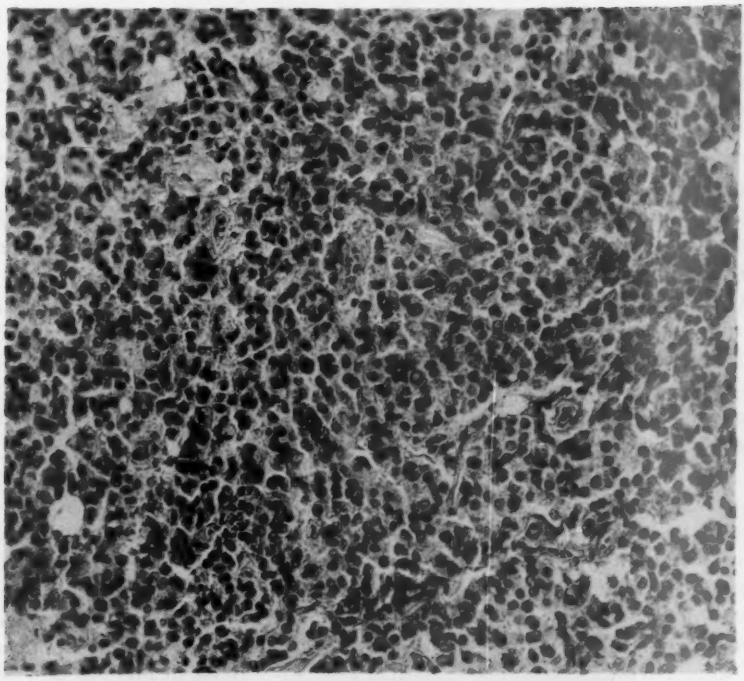


FIG. 2. Photomicrograph of chromophobe adenoma in case of D. Z.

During this period his libido decreased markedly. His visual fields were normal. Roentgenographically, the sella turcica was ballooned. In December, 1945, a cystic pituitary tumor was found on exploration elsewhere. Ten cubic centimeters of bloody fluid were removed and a biopsy was taken. The operation was followed by x-ray therapy in December, 1945, March, 1946, January and February, 1947, March, 1951, and December, 1951.

In June, 1946, peripheral field examination revealed an early right superior quadrantanopsia, and paresis of the extraocular muscles of the left eye; however, in October and November, 1949, the visual fields were reported to be normal. In April, 1953, psychomotor seizures appeared, consisting of nausea accompanied by amnesia for events and difficulty in remembering the names of familiar objects and people.

He was first seen by us on December 28, 1953, and was placed on Dilantin for psychomotor seizures, with satisfactory results. At this time he had 4 mm. of proptosis of the left eye, with associated partial oculomotor and trochlear nerve palsies. The left optic disc showed moderate pallor, VOS 20/30 and VOD 20/20, with a partial left upper nasal quadrant defect. The patient was reluctant to have surgery performed. By early July VOS had decreased to 20/200, and a right superior homonymous quadrantanopsia was evidenced (figure 1).

The previous left frontal craniotomy was reopened more widely on July 15, 1954. The left optic nerve was smaller than normal and showed yellowish discoloration; it was displaced medially by a large, grayish, lobulated, cystic chromophobe adenoma (figure 2). After subtotal removal, exploration of the prechiasmatic

area and right optic nerve was possible. The right optic nerve was normal. The patient recovered nicely.

Postoperatively, cortisone and Dilantin were continued. The left oculomotor nerve palsy had become complete; however, visual acuity improved to VOS 20/70, and VOD remained 20/20. Due to persisting right superior homonymous quadrantanopsia and psychomotor seizures, ventriculography has been recommended to define the extent of residual tumor in the floor of the middle fossa, which will be explored by a lateral approach.

Mild horizontal nystagmus resulted from diminished visual acuity in one patient, and in two others the etiology was never apparent. Some authors have also described vertical and rotatory nystagmus.

One patient complained of unilateral anosmia on the side of severe visual acuity loss. In two instances complete bilateral anosmia was obtained, in one case being secondary to carcinoma of the nasopharynx and in the other to extension of a malignant chromophobe tumor. Thus anosmia in a sellar tumor would lead one to suspect subfrontal extension of the neoplasm which may be malignant.

The incidence of convulsive disorder is rare. It occurred as a primary symptom in only one patient, being manifested by psychomotor seizures secondary to temporal lobe extension of a chromophobe adenoma. Two patients developed generalized convulsions several years after surgery, while in a third the seizures immediately followed an exposure to 500 r of irradiation therapy, a dose no longer used. This patient became semicomatose for four days. No further fits occurred even following three more courses of milder irradiation. The patient was already blind in one eye when first examined. The visual field in her other eye remained essentially normal nine years later.

On occasion, cerebrospinal rhinorrhea may complicate the clinical picture of a pituitary adenoma. We have under observation a patient whose acromegalic symptoms had been present for nine years. His rhinorrhea, starting in the fall of 1953, subsequently was complicated by three episodes of meningitis which were cured only after intense antibiotic administration. Two years later his rhinorrhea persists in spite of an unsuccessful surgical attempt at its correction. The cribriform plates were packed bilaterally and a thorough inspection about the chiasmatic region revealed no fistula. We conclude, therefore, that the leak is behind the chiasm into the sphenoid sinus. The tumor in this case did not press upon the optic chiasm. Hypophysectomy, which would have been necessary to disclose the point of leakage, seemed unjustifiable. The question remains: Can his leak be controlled by attacking it through the sphenoid sinus?

The clinical diagnosis of a pituitary tumor depends upon recognizing characteristic visual and endocrinologic disturbances. The diagnosis is substantiated by the careful roentgenographic examination and interpretation of the sella turcica. Many articles have been written on sellar changes in cases of pituitary tumor. Although various authors have suggested

anteroposterior and vertical sella measurements which are slightly at variance, generally most authorities agree that an anteroposterior measurement of 15 mm. and a transverse of 8 to 10 mm. represent the upper limit of normal. The appearance of the sella turcica harboring a pituitary tumor is characteristically "balloon shaped," due mainly to advancement of the anterior wall and depression of the floor (figure 3).

Of our series, in one case only was the sella turcica considered as normal. In 92 instances, ballooning of the sella was mild in two, moderate in 34 and severe in 56. The sella was completely destroyed in seven cases. Posterior clinoidal process erosion was considered as being early in 18 cases and advanced in 46. Complete absence of the posterior clinoids was noted in 20

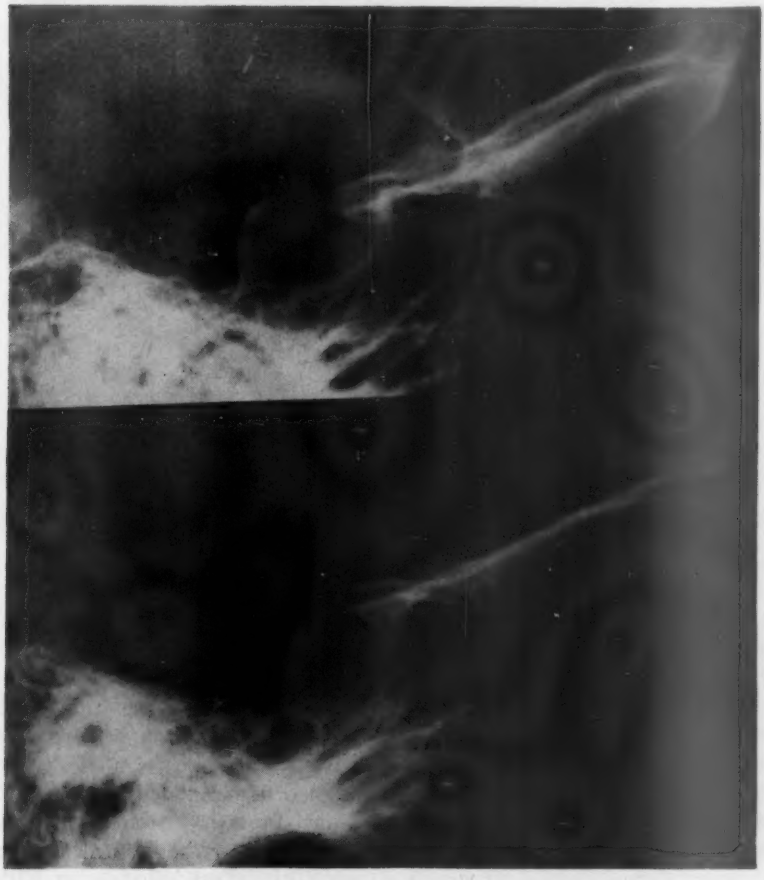


FIG. 3. Roentgenogram showing increase in size of the sella turcica over a five year period in a case of chromophobe adenoma.

instances. The anterior clinoids showed early erosion in five instances and advanced in four. Once they were entirely absent. The sphenoid sinuses were slightly invaded in 24 cases, and greatly so in 43. This was due to downward dipping and absorption of the floor of the sella turcica.

Camp [5] emphasizes the fact that basic bone changes such as decalcification, erosion and destruction may take place in and about the sella before any actual changes in size occur. He also stresses the capacity of the bone to recalcify after pressure is relieved. We have seen recalcification and



FIG. 4. Roentgenogram showing calcification within a pituitary tumor covering a 10 year period; visual fields normal.

reduction in size of an enlarged sella turcica in an acromegalic patient following irradiation of the adenoma, but never following irradiation of a chromophobe tumor.

In rare instances intrasellar calcification may develop in the tumor. This occurs within the sella, especially in chromophobe adenomas, less frequently in the suprasellar position. Calcification may take the form of flecks in the body of the tumor, or may appear as a dense, rounded shadow. The roentgenograms of one patient whose visual fields have remained normal under irradiation in spite of gradual enlargement of the sella for the past 10 years demonstrate a progressive degree of diffuse calcification within the tumor (figure 4). Another patient with a proved large chromophobe

adenoma showed a crescentic, calcified ring outlining the upper border of the tumor under the third ventricle (figure 5). In this instance an aneurysm of the internal carotid was originally suspected. Craniopharyngiomas likewise may frequently show areas of calcification. In such cases calcification is almost invariably in the body of the tumor rather than in the capsule of the sac. Schwartz [21] mentions the fact (also observed by others) that a large chromophobe adenoma may displace the pineal body backward.

We treated 66 patients surgically, with a total of 81 transfrontal operations, 15 of these operations representing reëxplorations. Ten additional

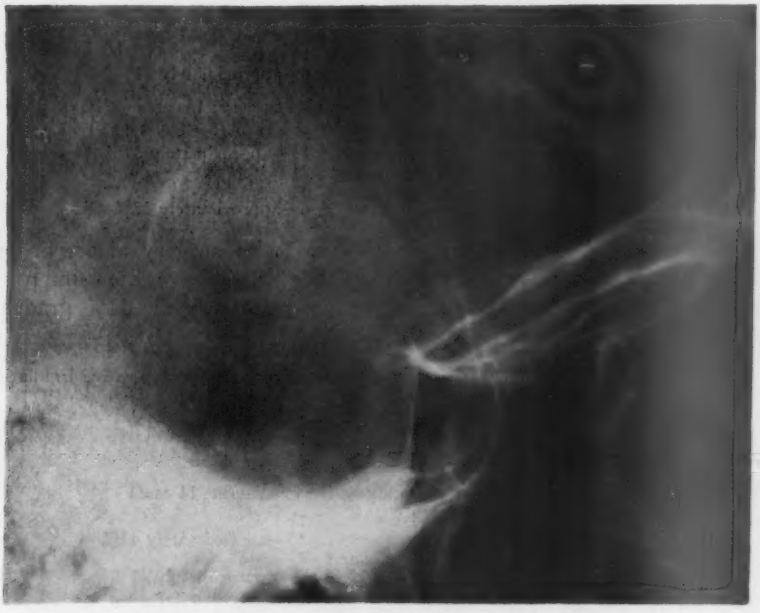


FIG. 5. Roentgenogram showing ringlike calcification of large chromophobe adenoma. Note entire erosion of dorsum sellae. Such a shadow is most often seen in aneurysm of internal carotid artery, or craniopharyngioma.

patients coming under our observation from time to time were operated upon by other neurosurgeons. Our over-all mortality was 7.7%. Causes of death: two from hyperthermia; one from cerebral edema one week after operation; one from gastrointestinal hemorrhage from injury to the hypothalamus; one from rupture of the cavernous sinus, and two from recurrent epidural and subdural clots.

The changes in visual fields following any type of treatment or combination of treatments do not run a course parallel to changes in visual acuity. Taken as a whole, the improvement in visual fields for a given number of cases (55.4%) is greater than relative improvement of visual

acuity (37.3%) in the same number of cases. If the visual fields became worse after treatment (42.1%), the visual acuity deteriorated even faster (57.8%). Fortunately, in a number of elderly patients the visual acuity could be considerably improved by proper refraction.

Our statistics, which are based upon personal follow-ups ranging from a few months to 25 years, with the majority being longer than five years, yield the following results:

1. Results of surgery alone: 19 cases

	Cases	
(a) Return to normal vision	6	
(b) Marked visual improvement	2	—approximately 63%
(c) Moderate visual improvement	4	
(d) Unimproved	1	
(e) Gradually worse	6	—approximately 31%

2. Results of preoperative irradiation plus surgery: 16 cases

(a) Return to normal vision	3	
(b) Marked visual improvement	1	—approximately 37%
(c) Moderate visual improvement	2	
(d) Unimproved	4	
(e) Gradually worse	6	—approximately 37%

Therefore, of the total number of cases with surgery alone, or preoperative x-ray and surgery, approximately 51% have been improved, about 14% unimproved, i.e., showing no progression, while 34% gradually became worse.

3. Results of preoperative irradiation, surgery and postoperative irradiation: 3 cases

(a) Improved	0
(b) Unimproved	1
(c) Gradually worse	2

4. Results of surgery and postoperative irradiation: 14 cases

(a) Return to normal vision	1	
(b) Marked visual improvement	1	—approximately 43%
(c) Moderate visual improvement	4	
(d) Unimproved	3	—approximately 21%
(e) Gradually worse	5	—approximately 36%

The following table gives our results where x-ray alone was employed:

5. Results of x-ray therapy alone: 32 cases

(a) Return to normal vision	8
(b) Marked visual improvement	6—approximately 62%
(c) Moderate visual improvement	6
(d) Unchanged	6—approximately 19%
(e) Gradually worse	6—approximately 19%

6. General conclusions

(a) Surgery alone	63% improved
(b) X-ray therapy alone	62% improved
(c) X-ray therapy and surgery	37% improved
(d) Surgery and x-ray therapy	43% improved

There has been an increasing tendency to employ irradiation in the treatment of pituitary tumors before resorting to surgery. Indeed, some clinics

employ irradiation exclusively in the majority of their patients. In the present series the results of surgery and x-ray therapy alone were almost identical; however, it must be pointed out that where x-ray therapy failed, a significant group of patients (37%) later was improved by surgery. In most instances postoperative irradiation was used only when recurrent symptoms developed in varying periods of time following surgery. Thus in a majority of cases the employment of irradiation was delayed for several years. Irradiation immediately after surgery was reserved for those with excessively large or malignant tumors. Figures as low as 32% [8] and as high as 85% [15] have been reported as representing the degree of satisfactory results obtained from irradiation alone. In the latter instance, rotational technic using a 2,000,000 voltage source was employed.

We believe that, in general, unless there is marked or rapid deterioration of the visual fields or acuity, a course of x-ray therapy should be tried first, keeping in mind the possibility of aggravation of the visual disturbances by acute edema or hemorrhage into the tumor, which might require immediate surgery. Further, one must remember that approximately 20% of tumors are cystic and respond poorly, if at all, to irradiation. The possibility of waiting too long before surgery always exists. This is particularly true of cystic tumors. Postoperative irradiation has become routine in most clinics. There is little doubt that in the majority of cases surgery and radiation, either immediately or delayed, give better results as to survival and recurrences than does surgery alone.

Horrax et al.[16] cite only 10% recurrence in five years after subfrontal exploration and irradiation, and 20% following transsphenoidal approach. We have two patients who have survived 23 and 25 years, respectively, with essentially normal fields and visual acuity, following only one course of x-ray therapy each. Interestingly enough, each of them had refused surgery, which was first proposed to correct his bitemporal defect. One man suffering from a mild form of acromegaly received 19,304 r over a period of 10 years, from October, 1931, to October, 1941. In spite of the massive amount of total radiation, he apparently sustained no ill effects and vision was preserved until his death from meningitis, which was attributed to erosion of the floor of the sella and extension of the tumor into the sphenoid sinus. Aside from this case, and the woman who received 500 r in one dose, our series has varied from 1,218 r to 10,500 r, with an average of 4,500 r measured in air. The average dose per course has been 2,485 r measured in air.

Heuer [13] has described beautifully the evolution of surgical approaches which have led up to the present transfrontal operation employed by the majority of neurosurgeons. This approach affords excellent exposure of the optic nerves and chiasm. If the approach remains extradural to the sphenoid ridge, where the dura is opened, little if any damage to the frontal lobe should occur. Sufficient credit, however, has not been given Hirsch [14]

for his skill in attacking pituitary tumors by the endoseptal approach. Up to 1951 he had operated upon 314 cases and probably has performed more since. The transsphenoidal approach has limited possibilities. It is most useful for tumors which grow downward into the sphenoidal sinuses. At best, only the floor of the tumor can be opened and a gutter type of partial removal accomplished. The optic nerves are never visualized. Cysts, however, may be successfully drained by this method. There is no opportunity of attacking extrasellar extensions of the tumor, if such exist. The mortality rate even before the days of antibiotics was low, and should be lower today. The main objection is not so much the danger of approach, for that is extradural, as the fact that one's operative field is limited, and less can be accomplished in the amount of tumor removal than by the transfrontal route. Sachs, in discussing Hirsch's paper, summed up the attitude of many neurosurgeons by saying "Neurosurgeons are more at home in the cranial cavity."

Nevertheless, it is to be remembered that Cushing, after employing the transsphenoidal route from 1912 to 1929, chose the transfrontal approach thereafter because of limited surgical possibilities of the former with regard to extrasellar extensions of tumor. The lateral approach, along the sphenoid ridge, routinely advocated by Kahn,[18] is necessary only for removal of temporal lobe extensions. A more direct approach through the orbit and ethmoid has been described by Chiari [6] and Smith.[22] The operation is said to be less deep, and bloodless in the sitting position; it gives excellent exposure, and can be accomplished in less than one hour. Few neurosurgeons, however, have endorsed it.

The authors' operative mortality for primary intrasellar removal of tumor was 7.4%. The over-all mortality for all cases seen by us, including as well those other neurosurgeons operated upon, was 7.7%. The causes of death were hypothalamic disturbance, cerebral edema, epidural and subdural hematoma, and rupture of the cavernous sinus.

The operative mortality in this review compares favorably with others. In 1948 Grant [10] reported 9.4%; in 1950 Bakay [2] noted in Olivecrona's series 11.3% (chromophobe) and 9.5% (chromophil). Jefferson [17] in 1940 and Younghusband et al.[24] in 1952 reported 2% and 3.9% mortality. Cushing's over-all operative mortality from transsphenoidal operations as reported by Henderson [12] in 1939 was 5.3%, and for transfrontal, 4.5%. During the last 10 year period he reduced the mortality from the transfrontal operation to 2.3%. For large extrasellar extensions the mortality percentage for most authors lies between 30 and 35%.

The pathologic picture of the surgical or autopsy material of the benign pituitary tumors and even the malignant adenomas in our series seemed to be rather characteristic. Of recent interest is a report by Antoni,[1] in which he claims that eight of 10 chromophobe adenomas were actually gliomas of the ependymal type. Also of interest are the reports of Wise et al.[23] and

others, describing the occurrence of various gliomas (oligodendroglioma, glioblastoma multiforme and cerebellar angioblastoma) in conjunction with pituitary tumors, a point always to keep in mind.

Although much has been written on the subject of "pituitary apoplexy," a condition brought on by sudden massive hemorrhage and necrosis within the body of a pituitary tumor (figure 6), the syndrome is not well known. The majority of cases exhibit fulminating symptoms identical with those of spontaneous subarachnoid hemorrhage, namely, severe headache, stiffness of the neck, nausea, vomiting, ophthalmoplegia, blindness in one or both

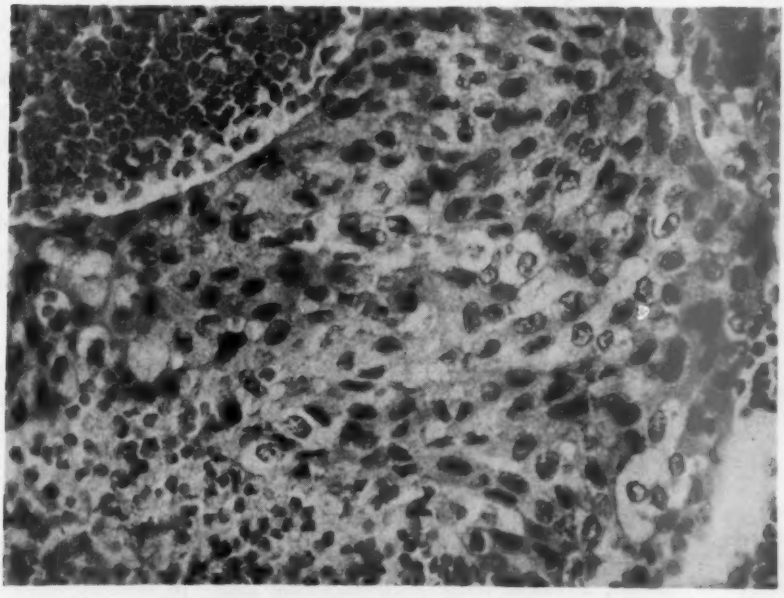


FIG. 6. Photomicrograph showing fresh hemorrhage into chromophobe adenoma—"pituitary apoplexy."

eyes, stupor progressing to coma, and usually death within a few hours. All patients, however, do not die. Spontaneous recovery or recovery by surgical decompression has been reported. The accident may be spontaneous or precipitated by trauma. In every instance the rupture of a cerebral aneurysm must be excluded. Because we have come to realize that "pituitary apoplexy" may be the cause of spontaneous subarachnoid hemorrhage in patients suffering from this syndrome, we now have x-rays of the skull taken as soon as possible upon admission to the hospital in order to ascertain the size, shape and condition of the sella turcica. When pituitary apoplexy has been diagnosed by the presence of an enlarged sella turcica, immediate exploration of the pituitary gland is imperative, along with

administration of cortisone or its related compounds; time is too short to permit extensive preoperative studies of variations in hormonal changes.

The advent of hypophysectomy in cases of malignant disease has shown that life may be maintained in the absence of the pituitary gland by the substitution of ACTH, cortisone and other appropriate hormones. In view of the supportive action of these hormones, which are now readily at hand, surgeons in the future may be tempted to remove pituitary tumors more radically than has been done in the past without undue concern about increased endocrine deficiency. Regardless of whether one plans to treat a patient harboring a pituitary tumor initially by irradiation or surgery, a decision which depends largely on the status of the visual acuity and fields and the biologic behavior of the tumor, it is important to investigate and correct by substitute hormonal therapy the hypoactivity of various endocrine glands, with particular emphasis on the adrenal and thyroid glands. The necessary tests and method of treatment have recently been outlined by several authors.[4, 11, 10]

Cerebral pneumoencephalography and angiography are the most accurate ways of determining the extent and direction of intracranial growth of pituitary tumors, and should be resorted to more frequently, as advocated by Gurdjian et al.[11] and List.[10] With the use of the partial-filling pneumoencephalographic technic of Bakay and White,[3] it is possible to follow the progress of the effects of irradiation on a pituitary tumor.

As with any other neoplastic disease, the end results with regard to the patient's symptoms and longevity depend upon early diagnosis, the type of tumor present, and appropriate treatment.

Summario in Interlingua

Es presentate un revista de 100 tumores pituitari que esseva observate per le autores. Sexanta-cinque del patientes esseva masculos con etates de inter 10 e 80 annos. Trenta-cinque esseva femininas con etates de inter 14 e 64 annos. In iste gruppo de tumores, 37 esseva verificate chromophobos solide, 10 verificate chromophobos cystic, 14 non-verificate chromophilos (acromegalic), 9 verificate chromophobos maligne primari, e 2 verificate carcinomas metastatic, le un con origine pectoral e le altere con origine nasopharyngee. Octanta-un operationes esseva executate in 66 patientes. Dece-cinque de istos representava re-explorationes. Le mortalitate operatori total esseva 7,4 pro cento. Le melioration del campos visual (55,4%) es plus grande que le melioration del acuitate visual (37,3%) in un date numero de casos. Es presentate un discussion general del meritos de chirurgia sol, de irradiation sol, e de chirurgia combinate con irradiation. Es delineate le tableau clinic general de disordines pituitari. Le calcification que occurre in tumores pituitari e le phenomeno del "apoplexia cerebral" es discutite. Le importantia del immediate tractamento chirurgic de iste ultime es signalate. Pneumo-encephalographia e angiographia representa le plus exacte medio visual pro estimar le dimension del tumores. Irradiation del tumor es recommendate si le alterationes del acuitate visual e del campo visual es moderate. Intervention chirurgic es recommendate in casos de serie hasardos pro le vision del patientes. In le majoritate del casos includite in le presente studio, un combination del duo methodos esseva usate. Le substitution de un appropriate therapia hormonal in omne casos es de importantia essential.

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CORTICOTROPIN AND ADRENAL STEROIDS AS ADJUNCTS TO THE TREATMENT OF TUBERCULOUS MENINGITIS *

By J. Richard Johnson, M.D., Nancy E. Furstenberg, M.D., Roy Patterson, M.D., Henry K. Schoch, M.D., and Winthrop N. Davey, M.D., *Ann Arbor, Michigan*

Introduction

The proposition that corticotropin and the adrenal steroids are worthy and often vital adjuncts to the antimicrobial therapy of certain infections has been strongly defended by some [1, 2] and just as strongly refuted by others.[3, 4] In this regard, it must be accepted that these hormones (if used alone) do reduce the resistance of many species of hosts to a wide variety of infections.[3] Experimental animal studies of combined hormonal and antimicrobial therapy, however, show little consistency as to results, even in the same species of animals.[5]

When using such combinations of drugs in clinical situations, the proponents of combined therapy assert that the antitoxic, anti-inflammatory and antifibrosing effects of the glucocorticoids are utilized to advantage. Simultaneously, the chemotherapeutic agents are given with the hope that they will effectively counterbalance those effects of the hormones which may be deleterious by depressing resistance to the infection, e.g., suppression of phagocytosis and antibody formation, blockage of the reticuloendothelial system and the general catabolic effect. The multiplicity of factors determining resistance and the variety of mechanisms involved in the development of various infections in different animal hosts have limited the applicability of experimental studies in animals in this regard. On the other hand, the enthusiastic clinical reports have been characterized as "empirical deductions in the absence of acceptable controls." [4] It would seem that the controversy could be settled only by properly controlled clinical trials.

A review of clinical experience with combined therapy in tuberculosis has revealed no apparent adverse effect upon the disease.[5] In pulmonary tuberculosis, however, where emergencies are less important than the long struggle to control the invading organism, the possibility of impairing antimicrobial action would ordinarily discourage the use of adrenal hormones.

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From the Medical Service, Veterans Administration Hospital, Ann Arbor, Michigan, and the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

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Requests for reprints should be addressed to J. Richard Johnson, M.D., Chief, Pulmonary Disease Section, Veterans Administration Hospital, Ann Arbor, Michigan.

Meningitis probably affords the best theoretic indication for the use of corticotropin or cortisone in tuberculosis. The still considerable mortality and high incidence of disabling neurologic sequelae justify the use of these potent agents if they are of value. Combined hormone-antimicrobial therapy in tuberculous meningitis has been reported by Shane and Riley,[6] Bulkeley[7] and Barnard.[8] It is being given to some of the most seriously ill patients in many places in this country and is in routine use in several European clinics.[9] Most feel the use of these hormones to be of value. Some do not, but no one has found that they have been harmful, with one possible exception.[10]

The closest approach to a controlled study to date is that of Ashby and Grant,[9] in which six consecutive patients were treated with antimicrobials alone in the usual manner, with the subsequent death of one patient following cerebrospinal fluid block, deafness in one, blindness in one, and hemiplegia in one. The next six cases were treated with the addition of cortisone for from three to five months. All recovered rapidly and completely.

Although theoretically ideal, a strictly random study in this disease is not likely to be accomplished. In the absence of such studies, the use of interrupted courses of hormones during routine antimicrobial treatment, with close observation of the effects on symptoms, neurologic status and cerebrospinal fluid examinations, would seem next best. Such interrupted courses of hormone therapy were employed in the first three of the five cases reported here. The first of these has been reported previously,[11] but is included again for comparison and follow-up. In one of the two cases reported by Kendig et al.,[10] the effectiveness of cortisone was demonstrated in a similar manner.

Case Reports

*Case 1.** The first patient was a 47 year old Negro male who had been confused and disoriented for at least three days prior to admission to the Veterans Administration Hospital but who was still able to complain loudly and bitterly of a "terrible headache." His neck and back were rigid and he was febrile. There was no other history or findings suggestive of tuberculous disease. The diagnosis of tuberculous meningitis was established on the basis of characteristic abnormalities in the cerebrospinal fluid, and treatment with a daily dosage of 2 gm. of streptomycin and 500 mg. of isoniazid was instituted. Subsequently, cultures of the spinal fluid demonstrated tubercle bacilli and the diagnosis was confirmed.

After four days of this routine treatment the disorientation, headache and stiff neck were unchanged, and there was progressive increase in the degree of fever and in the cerebrospinal fluid abnormalities. At this point (figure 1), treatment with aqueous corticotropin was begun. Complete remission of all signs and symptoms ensued over the period of the next 10 days. The dosage of corticotropin was reduced in a stepwise fashion over a three day period and then discontinued. Two days later there was an abrupt recurrence of headache, stiff neck and fever. The drug was resumed in full dosage, and again there was a complete remission of all signs and

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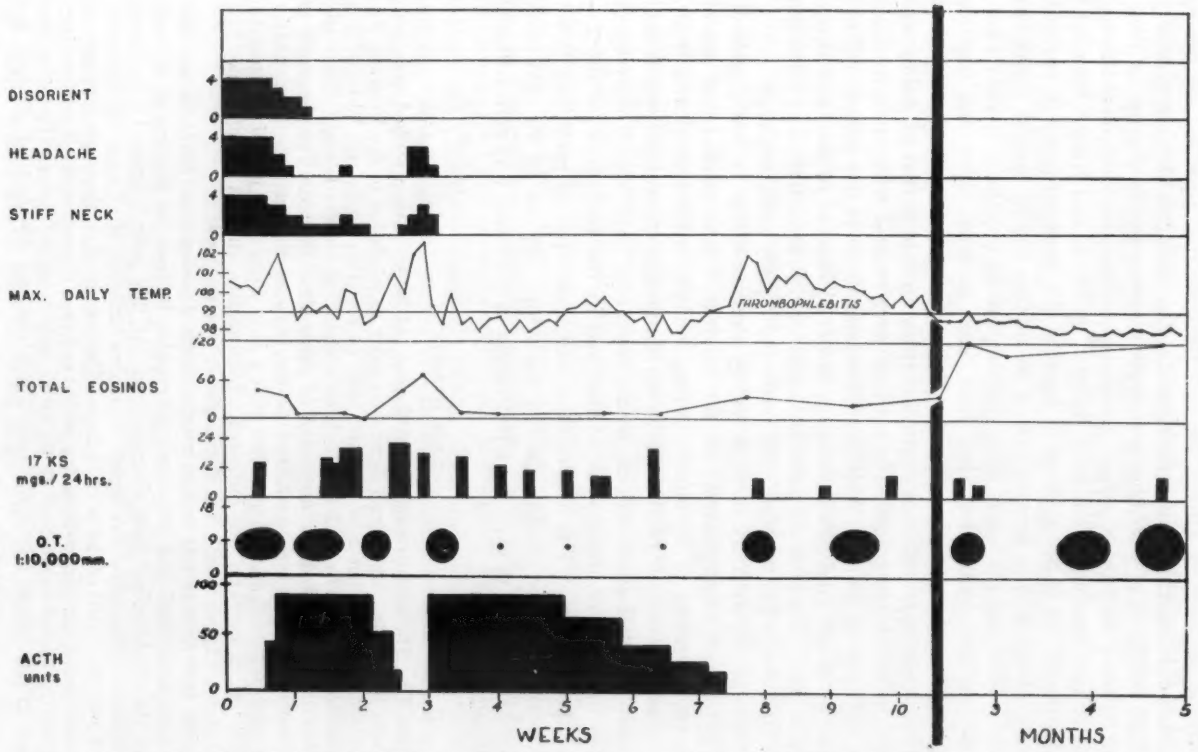


FIG. 1. *Case 1.* Relation of ACTH to clinical and laboratory findings. Courtesy of the *American Review of Tuberculosis and Pulmonary Diseases.*

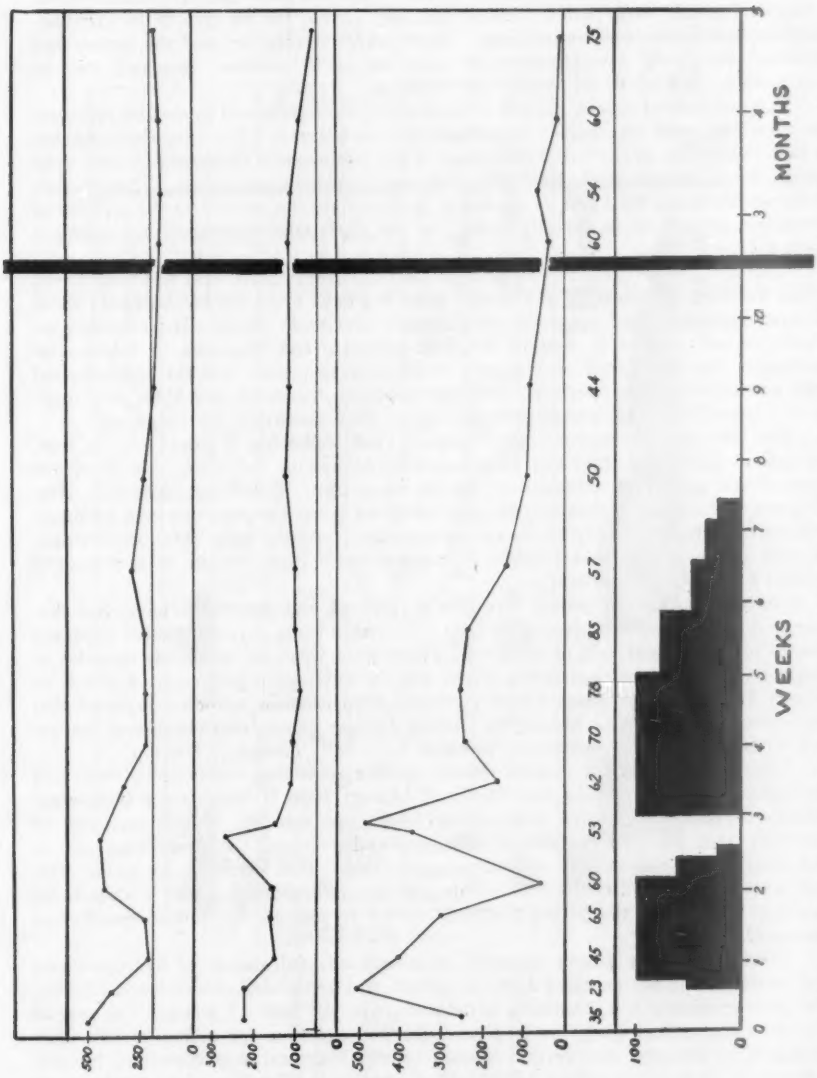


FIG. 2. *Case 1.* Relation of ACTH to cerebrospinal fluid changes. Courtesy of the *American Review of Tuberculosis and Pulmonary Diseases.*

symptoms in 24 hours. The dosage of corticotropin was then reduced gradually over a four and a half week period without difficulty, except for an episode of thrombophlebitis, which resolved uneventfully. There were no sequelae, and the patient has remained completely asymptomatic for a period of 18 months. Isoniazid will be continued for a total of 24 months of treatment.

Total eosinophil counts, urinary 17-ketosteroid excretions and tuberculin reactions are correlated with the courses of corticotropin in figure 1. The cutaneous reaction to Old Tuberculin in the 1:100 dilution was not significantly decreased in size, even though the reaction to the 1:10,000 dilution was completely suppressed. The pressure of the cerebrospinal fluid and its content of protein and cells, as well as the severity of symptoms, appears to be directly related to the interrupted courses of corticotropin (figure 2).

Case 2. The second patient was a 33 year old Negro male who was transferred to the Veterans Administration Hospital after five days in an outside hospital, where his symptomatology had suggested the diagnosis of a brain tumor. His condition on admission was similar to that of the first patient. The diagnosis of tuberculous meningitis was established on the basis of the clinical picture and the cerebrospinal fluid abnormalities, and treatment with streptomycin, isoniazid and PAS was instituted (figure 3). Again, culture of the spinal fluid confirmed the diagnosis.

For two days there was little change. Then, following a grand mal seizure, the patient failed to regain full consciousness and became delirious. He developed opisthotonos and became comatose. There were signs of left hemiparesis. After 18 hours without improvement, hydrocortisone was given intravenously and cortisone was started intramuscularly as emergency measures. At the same time corticotropin gel was begun, and it was planned to continue with corticotropin as a prolonged adjunct to antimicrobial therapy.

Within 24 hours the patient was able to respond and the opisthotonos had disappeared. The fever disappeared by lysis, and within three days the patient appeared normal for the greater part of the time. There were, however, persisting episodes of confusion, some nuchal rigidity, a slight rise in total eosinophil count and fall of urinary 17-ketosteroids, coupled with continued hyponatremia. It was suspected that the corticotropin gel was lacking in potency or was being inactivated, and its use was discontinued. Hydrocortisone was used in a daily dosage of 200 mg.

After three weeks the patient seemed to have recovered nearly completely, and the dosage of hydrocortisone was decreased in a stepwise fashion over a three-week period. Despite progressive increase in fever, symptomatic relapse occurred so gradually that the patient became irrational and required the continuous use of restraints before the relapse was fully appreciated. This occurred 24 hours after hydrocortisone was discontinued and despite the intermittent use of corticotropin aimed at stimulating the patient's adrenal cortex to produce its normal quantity of hormones.

When the relapse became apparent, treatment with full dosage of hydrocortisone was resumed, and within eight days the patient was again well oriented and afebrile. The hydrocortisone was gradually withdrawn over the next 11 weeks. On several occasions the patient complained of headache and agitation for a day or two after reduction in dosage. For several months after withdrawal was completed he also complained of these symptoms on numerous occasions. Some residual weakness of the left leg remained but the patient was essentially asymptomatic at the time of discharge, 10 months after admission. He remains well six months after discharge.

The laboratory findings are again seen to correlate with the steroid administration (figure 3). Of interest was the failure of a daily dosage of 100 mg. of hydrocortisone to reduce the total eosinophil counts. The depression of urinary 17-ketosteroid excretion and the incomplete suppression of the tuberculin reaction by

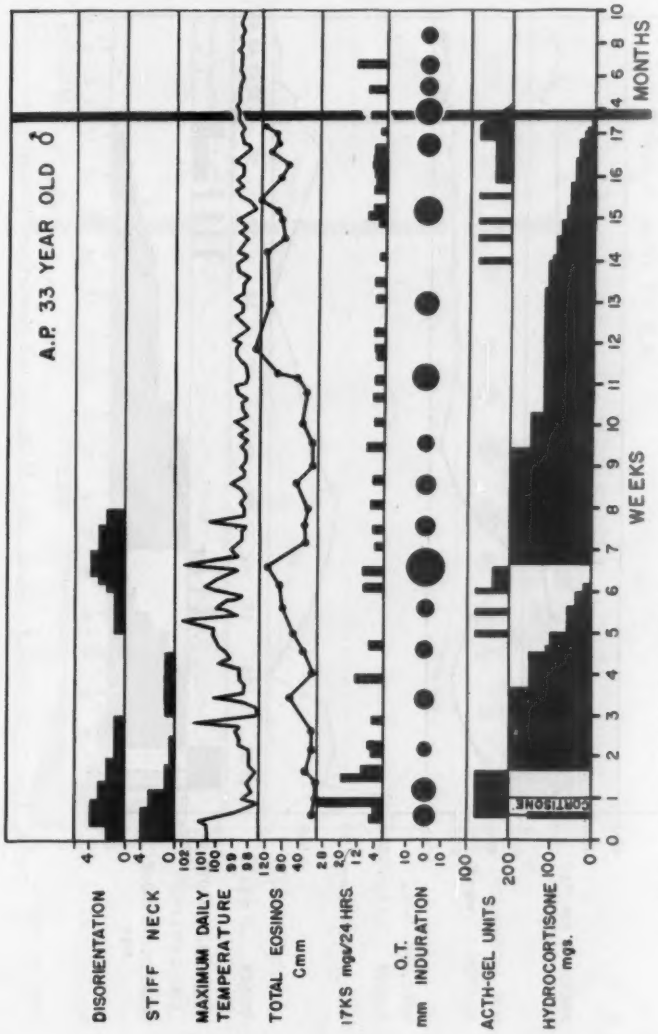


FIG. 3. *Case 2.* Relation of clinical and laboratory data to hydrocortisone therapy.

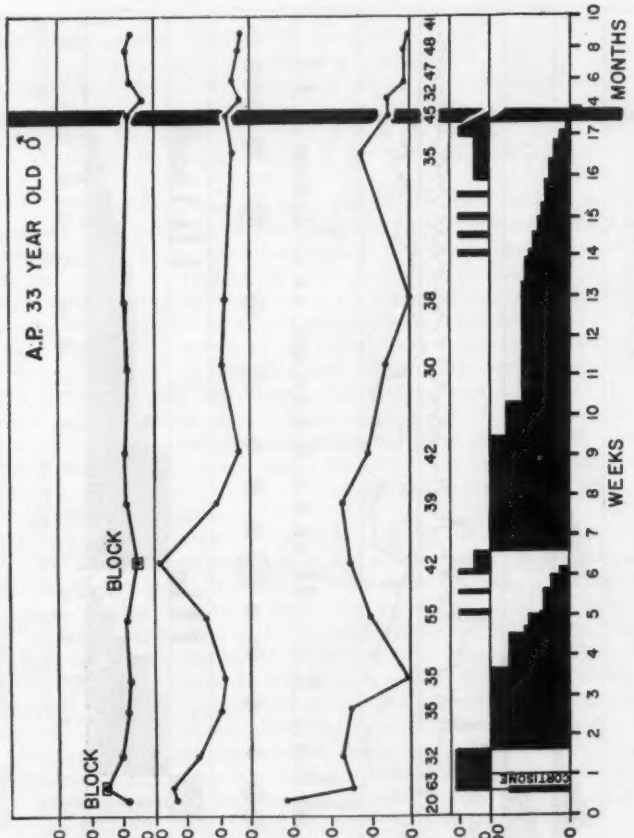


FIG. 4. *Case 2.* Relation of cerebrospinal fluid changes to hydrocortisone therapy.

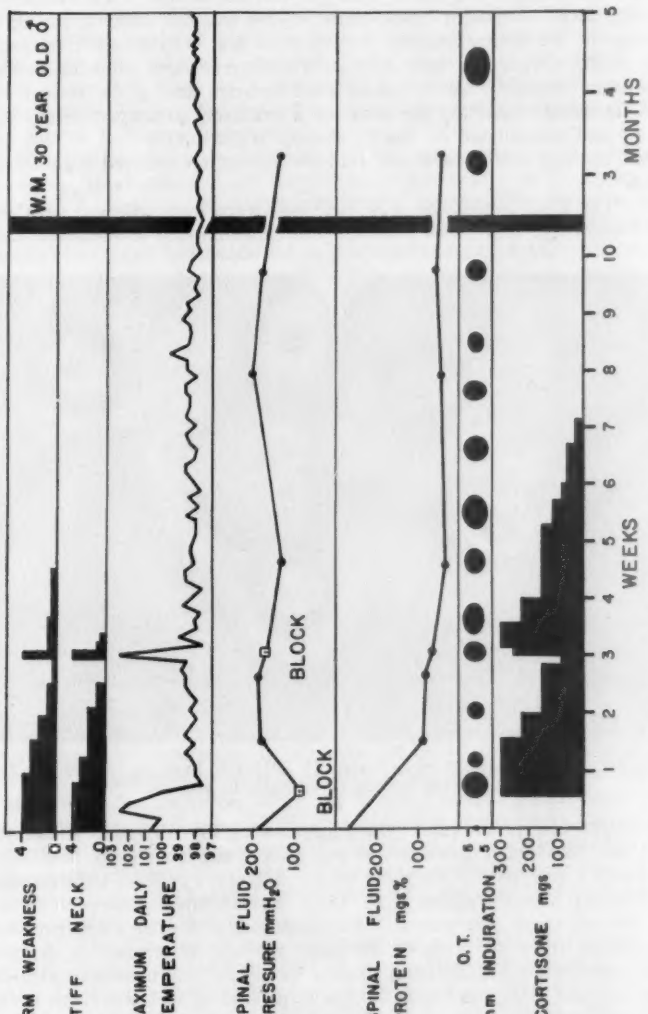


FIG. 5. *Case 3.* Relation of clinical and laboratory data to cortisone therapy.

the hormone were noteworthy. Most significant, however, were the cerebrospinal fluid findings in relation to hydrocortisone therapy (figure 4). Cerebrospinal fluid block was discovered following the grand mal convulsion during the initial control period on antimicrobials alone, and it recurred with the relapse when hydrocortisone was first withdrawn. Although symptomatic relapse was not detected during reduction in dosage of the hydrocortisone, both protein and cells foretold relapse upon withdrawal of the steroid and were correlated with remission following resumption of hydrocortisone therapy. Cerebrospinal fluid findings during the second attempt at reduction in dosage indicated the need for a relatively prolonged period of combined therapy and necessitated the use of steroids for a total period of four months. Antimicrobial therapy will be continued until the patient has received a full 24 months of treatment.

Case 3. The third patient was a 30 year old Negro male who had been successfully treated elsewhere four years previously for disseminated tuberculosis involving

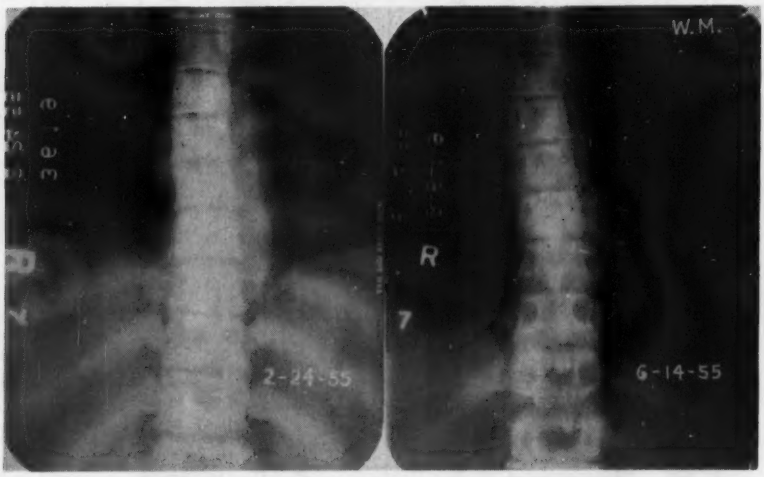


FIG. 6. *Case 3.* Laminagrams of February 24, 1955 and June 14, 1955 at the 7 cm. level showing healing of paraspinous abscess.

the ribs, kidneys and peritoneum. On admission to the Veterans Administration Hospital he was febrile and demonstrated paralysis of the left triceps, scoliosis and a torticollis due to a stiff, painful back and neck. Babinski's reflexes were questionably present bilaterally. Cerebrospinal fluid block and elevated protein content were found, but the cell count was normal. Roentgenograms showed a left paravertebral abscess extending from the sixth to the tenth thoracic vertebrae. A diagnosis of epidural and paravertebral tuberculous abscess was made, and treatment with streptomycin, isoniazid and PAS was begun. After three days of such treatment the patient showed no improvement in paralysis, pain or stiffness, and there was increase in the degree of fever. There was persistent hyperactivity of the deep tendon reflexes of the lower extremities. When cerebrospinal fluid block was demonstrated on the third day, oral cortisone was administered in a daily dosage of 300 mg. (figure 5).

Twenty-four hours after the institution of steroid therapy, the fever and pain were gone and the patient felt much better, being able to lie comfortably in bed. The next lumbar puncture one week later revealed no evidence of block, and a

definite reduction in protein content of the cerebrospinal fluid had occurred. Ten days after the start of cortisone treatment this patient was without sign or symptom, and reduction in dosage of the cortisone was begun. After one week the daily dosage of cortisone was reduced from 150 to 75 mg., and by the next morning the patient became symptomatic. Over a period of four hours there developed complete paralysis of the left triceps, a painful torticollis and scoliosis, and a fever of 102° F. Lumbar puncture again demonstrated a complete block. Increase in the dosage of cortisone to 75 mg., given four times daily, resulted in nearly complete relief of all symptoms and signs within 24 hours, and the cerebrospinal fluid examination one week later was entirely normal, without evidence of block.

This patient subsequently remained without symptoms or signs, despite gradual withdrawal of the hormone over the period of the next month. Being completely asymptomatic for four months, the patient became increasingly restive and left against medical advice five months after admission. Ten months later he reported himself to be entirely well and had continued to take isoniazid and PAS. The paravertebral abscess had practically disappeared from view in one month on routine x-ray examination. Laminagrams obtained after four months of treatment confirmed the very definite improvement (figure 6). No definite osseous lesion was detected in the dorsal or cervical spine.

Case 4. The fourth patient was a 39 year old white male who had been treated elsewhere for pulmonary tuberculosis and chest wall abscess from 1947 to 1949 and had received irradiation therapy for tuberculous cervical adenitis in 1950, 1952 and 1953. On admission to the University Hospital (figure 7) he was stuporous, incontinent and markedly febrile. There were papilledema and nuchal rigidity. Cerebrospinal fluid examination showed the typical findings of tuberculous meningitis. This diagnosis was later confirmed by culture of the spinal fluid. X-ray examination of the chest demonstrated widespread miliary lesions. Treatment was begun with streptomycin, isoniazid and pyrazinamide, and the patient was fed by gavage. For one month this treatment was continued without clinical improvement. The patient remained stuporous and was unable to turn in bed or feed himself. There developed a ptosis of the left lid. The fever abated and then returned to pretreatment levels. Cerebrospinal fluid content of protein and cells showed a definite improvement, but the spinal fluid sugar remained low. Corticotropin was then administered intravenously, in a dosage of 20 mg. daily. On the second day the patient recognized his family and talked to them. He helped to feed himself and to turn in bed. Attempts to reduce this dose even slightly over the next two weeks resulted in prompt recurrence of mental confusion. On as little as 20 units of corticotropin gel twice daily (and later 15 units twice daily), the patient's mental status steadily improved. The ptosis disappeared, leaving slight diplopia on near vision as the only residual. The patient gained 60 pounds in weight and regained control of bowel and bladder. The pulmonary lesions resolved and the temperature remained normal. The patient was discharged from the hospital 14 months after admission and has remained well to the present time, nine months after discharge.

Case 5. The fifth patient was a 71 year old white female who was comatose, markedly febrile and severely depleted of electrolytes at the time of admission to University Hospital. She had been seriously ill for 20 days before the diagnosis of tuberculous meningitis was established and before treatment with streptomycin and isoniazid was begun. Physical examination showed a blood pressure of 168/92 mm. of Hg, marked nuchal rigidity, bilateral Babinski's reflexes and cogwheel rigidity of the right arm. No papilledema or pupillary abnormality was present. Cerebrospinal fluid examination demonstrated an initial pressure of 320 mm. of water and a sugar content of 9 mg.%. Cultures for pyogenic organisms were negative, but those for tubercle bacilli were positive. Confirmation through guinea pig inocu-

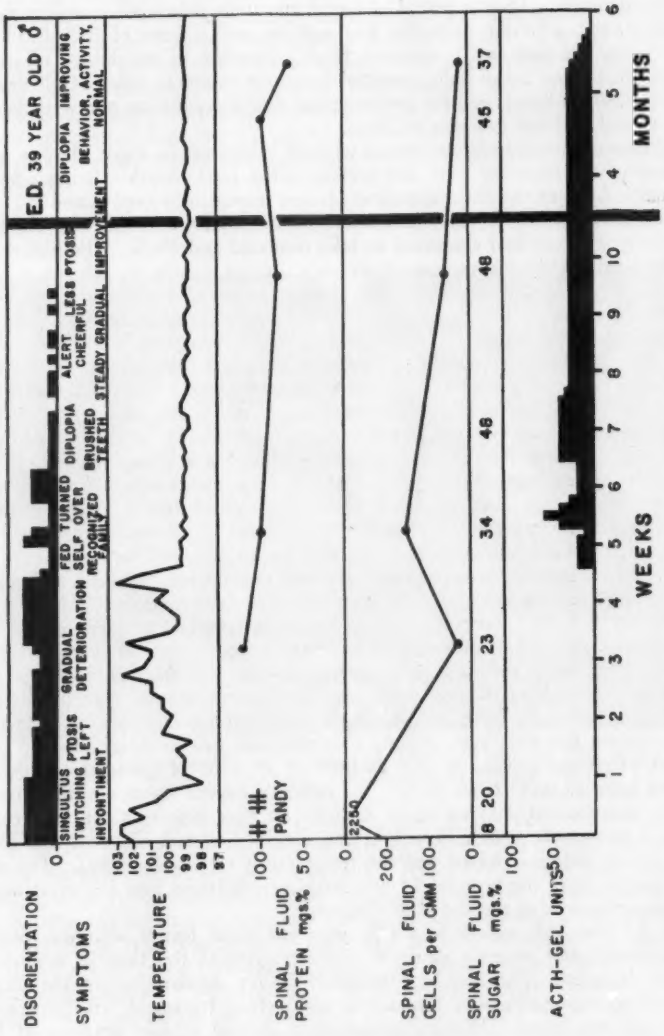


FIG. 7. *Case 4.* Relation of clinical and laboratory data to corticotropin therapy.

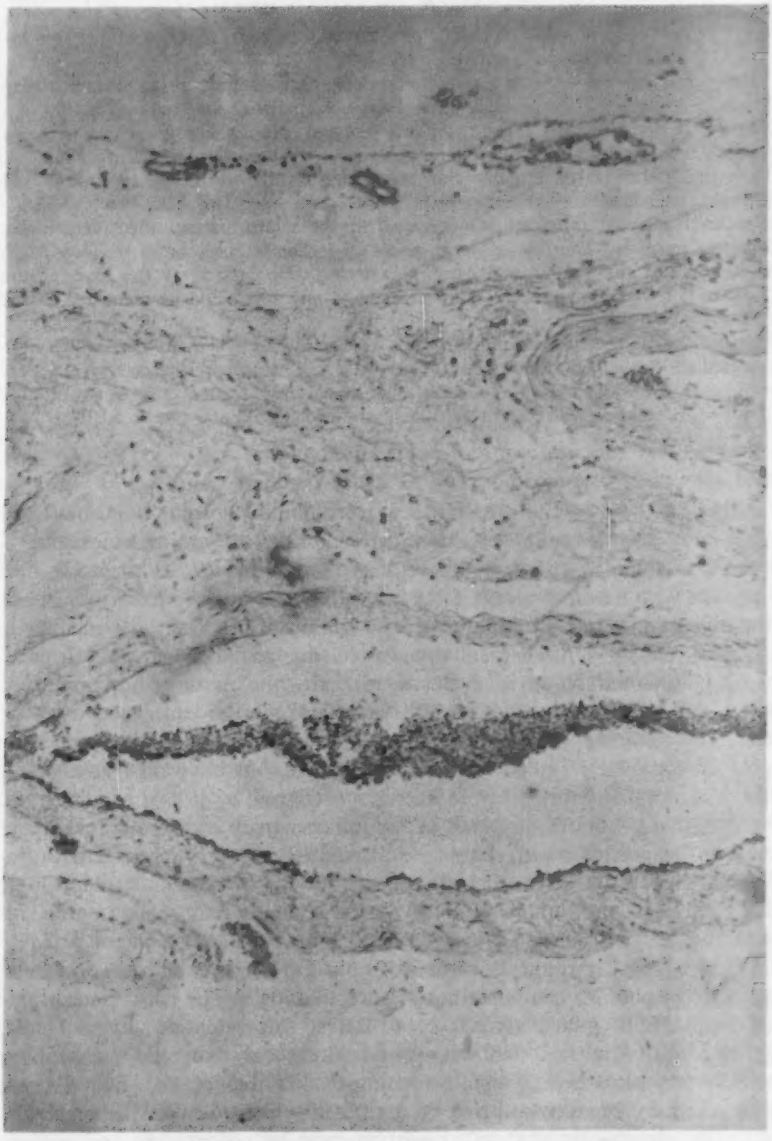


FIG. 8. *Case 5.* Old healed leptomeningitis. No tubercles found. No exudate.

lation was reported later. The chest roentgenogram revealed no significant abnormality. Serum sodium values of 107 to 122 mEq./L. were found. Carbon dioxide combining power was 23 to 32 mM/L. Serum potassium and blood nonprotein nitrogen values were normal. The cutaneous reactions to 1/10,000 and 1/100 dilutions of Old Tuberculin were negative.

There was no response to chemotherapy or to the addition of intramuscular cortisone in dosage of 200 mg. Later the dosage of cortisone was reduced to 100 mg. daily, given in divided doses. The fever was less and serum electrolyte concentrations were more nearly normal after cortisone was added. The patient remained comatose and eventually died three months after admission as the result of aspiration and suppurative pneumonitis. At autopsy there was some edema of both cerebral hemispheres and scattered petechial hemorrhages of the white matter. The ventricular system was normal. There were large areas of ischemic necrosis in the cerebrum, with sclerosis of the basilar and cerebral arteries. No lesions at the base of the brain were noted and, in particular, no exudate of any sort could be identified as the residual of meningitis.

On microscopic examination there was thickening of the meninges, which was interpreted as healed leptomeningitis (figure 8), but no tubercles and no exudates were found. The tuberculous infection had apparently healed after two months of combined treatment with cortisone and antimicrobial agents.

Comment

Although there is the possibility that combined hormone-antimicrobial therapy may sacrifice some of the effectiveness of the antimicrobials, it is felt there is some to spare in tuberculous meningitis. It is probable that the patient who becomes worse after antimicrobials are begun is dying, not of the infection, but of the inflammatory reaction of his brain and meninges. It is, then, chiefly a mechanical catastrophe due to blockage of both cerebrospinal fluid and blood in a closed space by the mass of inflammatory exudate and granulations. The fifth case, and similar autopsied cases of others,[6, 7, 10] indicate that patients succumbing under chemotherapy have largely or completely healed the infection per se, but have died as a result of the hydrocephalus or ischemic necrosis produced by it. It would seem, therefore, that partial suppression of the inflammatory exudate with adrenal hormones or corticotropin should be attempted in every patient with tuberculous meningitis where there is concern for life or permanent neurologic damage, at least until there is some direct evidence that there is any significant hazard with such adjunctive therapy in tuberculous meningitis.

When adrenal hormones or corticotropin are used, close attention must be paid to the possible complications of such therapy. The usual precautions must be taken to guard against or to detect salt retention, hypokalemia, aggravation of diabetes mellitus, peptic ulcer and pyogenic infections—especially superimposed pyogenic meningitis. Three of our five patients had marked hyponatremia prior to treatment—the so-called cerebral salt wastage syndrome—so that salt retention may be no problem and sodium supplements may even be needed at first.

In general, the following routine was employed in our patients. Daily

weights were recorded and the salt content of the diet was restricted. These patients were given 6 gm. of potassium chloride daily, antacids for any minor gastrointestinal distress, and 1 gm. of a tetracycline daily during the period of full hormone dosage. Serum electrolytes and fasting blood determinations were performed weekly.

Both short courses (e.g., one to five weeks [1, 7]), and long courses (three to 12 months [6, 8, 9]) of adjunctive hormone therapy have been employed. Two of our patients required only seven weeks and two a little over four months of such treatment. It is suggested that treatment with *full* dosages of the hormones be continued until the patient is asymptomatic, or for a maximum period of two to three weeks. The dose may then be reduced over a period of one week to approximately half the previous level. This new dose should then be maintained as long as there is continuing significant improvement either in the patient's condition or in his cerebrospinal fluid. When the patient is asymptomatic or shows no further improvement, the hormone may be discontinued gradually over a two- to three-week period. In our second patient, more than one month was required for this last step, and corticotropin was employed to assist in adrenocortical recovery.

Our first patient relapsed when the corticotropin was entirely discontinued in the third week of combined treatment. The third patient also relapsed in the third week when cortisone was reduced from 50 mg. to 25 mg. three times a day. After three weeks of treatment, when the hydrocortisone was reduced from 200 mg. to 150 mg. per day, the second patient showed slight temperature elevation as the first sign of his subsequent relapse. It would appear that from one to four months of treatment is advisable to maintain the early gains if setbacks are to be avoided.

We have used the term "full dosage" to mean intramuscular aqueous corticotropin in a dosage of 25 units every six hours (or corticotropin gel, 40 units every 12 hours), cortisone, 300 mg., or hydrocortisone, 200 mg. daily in four divided doses orally. The relative advantages and disadvantages of corticotropin versus the corticosteroids have been discussed elsewhere.[11] The drug of choice may well prove to be prednisone or prednisolone, which has relatively more glucocorticoid and hence more anti-inflammatory effect, with relatively less of the mineralocorticoid effects.

It must be emphasized that the essential part of treatment is the specific antimicrobial therapy. We have used 6 to 8 mg. of isoniazid per kilogram of body weight daily, plus 1 gm. of dihydrostreptomycin and 1 gm. of streptomycin daily, usually in association with calcium or potassium para-aminosalicylate, in a dosage of 12 gm. per day. When full recovery is assured the dosage of streptomycin is reduced to 1 gm. of either streptomycin or dihydrostreptomycin daily, and eventually to 1 gm. twice weekly. After discharge from the hospital the patients continue on 300 mg. of isoniazid daily and 12 gm. of sodium para-aminosalicylate until a total of two years of chemotherapy has been completed.

Summary

Corticotropin, cortisone and hydrocortisone given in interrupted courses are shown to be correlated directly with marked improvement of symptoms, signs and cerebrospinal fluid findings in three cases of tuberculous meningitis. In a fourth patient, improvement did not occur during one month of routine chemotherapy but became apparent the day after corticotropin was begun. The fifth patient, comatose and in her seventies, had irreversible brain damage, but necropsy revealed complete gross and microscopic healing of her tuberculous infection after two months of cortisone-antimicrobial treatment. Each patient received continuous conventional streptomycin and isoniazid therapy.

These five cases are believed to demonstrate the value of combining adrenal hormones with antimicrobial therapy in the treatment of tuberculous meningitis.

Summario in Interlingua

Cinque patientes sub tractamento antimicrobial pro demonstrate meningitis tuberculotic esseva studiate pro determinar le effecto producite per le addition de corticotropina, cortisona, o hydrocortisona al regime therapeutic.

Tres del patientes recipeva cursos interrumpite de iste hormones. Le tractamento esseva instituite post un breve periodo initial de therapia a streptomycina e isoniazido. Durante iste periodo nulle alteration o clar pejoration del condition del patiente esseva notate. Le addition de corticotropina, cortisona, o hydrocortisona esseva sequite per prompte remission clinic e un retorno rapide del alterationes in le fluido cerebrospinal a lor stato normal. Le interruption del curso de hormones post duo o tres septimanas resultava in prompte recidivas clinic e le pejoration del constatationes in le fluido cerebrospinal. Le re-institution de ille drogas esseva de novo sequite per remissiones immediate. Le elimination gradual del therapia hormonal in le curso del subsequente quatro a 12 septimanas esseva effectuate sin recidiva.

Le quarte patiente habeva remanite disorientate, incontinente, e febril post un mense de tractamento con streptomycina, isoniazido, e pyrazinamido. Le addition de corticotropina esseva accompaniate per prompte e remarcabile melioration. Le curso hormonal esseva terminate sin difficultate post un intervallo de quatro menses.

Le quinte patiente, de 70 annos de etate, habeva essite seriemente malade durante tres septimanas. Ille esseva comatose quando le therapia antimicrobial esseva comenciate. Cortisona esseva addite un septimana plus tarde, sed le patiente remaneva comatose e moriva tres menses plus tarde ab pneumonia per aspiration. Al necropsia, areas necrotic esseva trovate in le cerebro, sed le meningitis se monstrava subjugate sin residuo grossier o microscopicamente specific.

Es presentate graphicos in que datos clinic e laboratorial es correlationate con le curso del therapia hormonal. Es etiam illustrate le processo curative de un abscesso paraspinose in le tertie patiente e del meningitis basal in le quinte patiente.

Le conclusion es formulate que le cinque patientes del presente reporto demonstra le valor del combination de drogas hormonal e antimicrobial in le tractamento de meningitis tuberculotic.

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ACTH AND CORTISONE AS ADJUNCTS IN THE TREATMENT OF ADVANCED PULMONARY TUBERCULOSIS *

By PETER ELSBACH and JOHN R. EDSALL, *New York, N. Y.*

IN recent years it has been shown that the addition of steroid hormones to antimicrobial treatment can be beneficial in the management of overwhelming infections due to such organisms as meningococci, pneumococci, salmonellae, brucellae or klebsiellae.[1-4]

There has been little description of such combined treatment of severe tuberculosis in the American literature. Most authorities have pointed out the hazards of steroid therapy in the presence of active tuberculosis [5-7] except in tuberculous meningitis, where steroids are now part of the accepted management.[8, 9] This fear was first aroused when the use of steroids for nontuberculous diseases led to the activation of a cryptic tuberculous focus, with severe and sometimes fatal outcome.[10, 11] The rare reports on the use of steroids for known tuberculous processes were also discouraging.[12] It should be emphasized, however, that such hormonal therapy was usually not covered by antituberculous drugs and, if such drugs were used, resistance was frequently present.[13]

In the foreign literature, mostly in French journals but also in those of Britain, Switzerland and Germany, mention has been made with increasing frequency of beneficial effects observed from the combination of antituberculous drugs and adrenocortical hormones in the treatment of various forms of advanced tuberculosis.[12, 14-20] The earlier reports also pertained to cases where steroids were used for nontuberculous diseases, such as lupus erythematosus, sarcoidosis or Hodgkin's disease, in which tuberculosis was known to be present and seen to regress under combined treatment.[21, 22] When it was found that steroid therapy for control of hypersensitivity reactions to the antituberculous drugs, or for Addison's disease in the presence of active pulmonary tuberculosis,[23] was followed by an unexpected improvement in several instances,[15, 17] a careful evaluation was attempted in isolated cases.[17]

Extensive experimental work has been done to study the effect of adrenocortical hormones on the response of the organism to bacterial infections and on antibody formation. The conclusions drawn have been conflicting,[7, 24-28] and it has been emphasized [15, 20, 29] that observations made in animal experiments cannot be applied to clinical situations. Experimental

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From the Third (New York University) Medical Division and First (Columbia) Division (Chest Service), Bellevue Hospital, New York, N. Y.

Requests for reprints should be addressed to Peter Elsbach, M.D., The Rockefeller Institute, York Avenue and Sixty-sixth Street, New York 21, N. Y.

infection with tubercle bacilli in many different species of animals demonstrated again the well known species-specific susceptibility to the acid-fast bacilli, as well as [23-25, 29] a species variation in the response to steroid administration, and also in endogenous hormone production.[30] Comparison of the results of the different investigators is furthermore hampered by the use of different strains of tubercle bacilli in inducing the experimental infection, and by the large doses of hormone administered, which exceeded by far the amount given to humans. It therefore appears that an evaluation of the usefulness of steroid hormones as an adjuvant in the treatment of pulmonary tuberculous infections can be arrived at only by careful clinical trial and observation. Controlled clinical studies employing larger series are not yet available.

The case histories of three patients will be presented, and the provisional impressions, derived from the limited case material so far reported, will be reviewed.

Case Reports

Case 1. A 64 year old white man was admitted to Bellevue Hospital on October 13, 1955, with a two-month history of increasing weakness and pain in the legs. He denied any other symptoms, apart from cough productive of small amounts of white sputum for many years. Alcoholism had existed for many years. He had had chronic leg ulcers which had caused difficulty in walking for two years.

Physical examination showed: temperature, 103.6° F.; pulse, 115, regular; respiration, 22, regular; blood pressure, 110/60 mm. of Hg. The patient was acutely and chronically ill, dirty and lice-infested, and his skin was covered with multiple excoriations. He was restless and confused. The chest was symmetrical, with equal respiratory movements. The percussion note was impaired over the front and back of the left upper lobe, in which area many moist râles and diminished breath sounds were heard. The heart was normal. The liver was palpable three fingerbreadths below the right costal margin. There was no clubbing of the fingers or toes. Three plus pitting edema of the legs reached the knees, and chronic anterior tibial ulcers were present. Neurologic examination, including funduscopy, was unremarkable.

On admission the white blood cell count was 6,500 with a normal differential count. Hemoglobin was 12.5 gm.%. Erythrocyte sedimentation rate was 46 mm./hr. (Wintrobe). Analysis of the urine was negative.

Chest x-ray on admission revealed a soft fluffy infiltrate extending from above the left third anterior rib into the hilum. There was a strong suggestion of cavitation in this area.

Treatment and Course: An initial diagnosis of pneumonia was made, and 250 mg. of tetracycline were given intramuscularly four times a day. On October 14 acid-fast bacilli were found in the sputum, and the patient was transferred to the Chest Service. The tetracycline was discontinued, and 1 gm. of streptomycin, 15 gm. of PAS and 1,800,000 units of procaine penicillin daily were started, with a drop in temperature to low febrile levels but no other clinical improvement. On October 27 isonicotinic acid was added because of the poor response. During this time the patient's mental confusion increased, delirium tremens developed, and he was transferred to the psychiatric medical ward. His general condition had markedly deteriorated. He was cyanotic and had to be placed in an oxygen tent, and tube feeding was started. X-rays showed an increase in cavitation in the left upper lobe, with spread of the disease to the left lower lobe. On October 29 the blood pressure

dropped to 80/60 mm. of Hg and the patient appeared to be moribund. Because of this, cortisone, 25 mg. twice daily intramuscularly, was started, without response. On November 1 the dose was raised to 100 mg. daily. Within 48 hours the patient was brighter, the temperature became normal, the tube was removed and oral feeding was begun. The blood pressure remained at 75/40 mm. of Hg. On November 5 further improvement was clinically striking. The blood pressure had risen to 100/70 mm. of Hg. From this time onward, apart from a bout of vomiting which responded to withdrawal of PAS, the patient showed continuous rapid improvement. The cortisone dose was gradually decreased and was discontinued between November 21 and 28 without relapse. The total dose of cortisone amounted to 1,375 mg., given in 31 days. The acid-fast bacilli cultured from the sputum were sensitive to all three drugs.

Case 2. A 53 year old Negro man, a long-standing alcoholic, was admitted to another hospital on June 28, 1955. Pulmonary tuberculosis was suspected, and treatment with streptomycin and penicillin was started. In the following weeks there was no improvement, and the patient became progressively more confused. On July 18 he was transferred to Bellevue Hospital.

Physical examination showed: temperature 101.6° F.; pulse, 104, regular; respiration, 20, regular; blood pressure, 105/75 mm. of Hg. The patient was severely ill, incontinent and totally disoriented. There were deep sacral decubital ulcers. Respiration was shallow. The percussion note was flat over the entire left chest, with absent breath sounds and diminished tactile and vocal fremitus in this area. The trachea was slightly displaced to the right. The heart also seemed displaced to the right. The sounds were distant. The liver was palpable three fingerbreadths below the right costal margin. Examination of the extremities and nervous system, including funduscopy, was unremarkable.

On admission the white blood cell count was 2,000, with a normal differential count. Hemoglobin was 4.5 gm.%. There was a trace of blood by the guaiac test in the stool. Serum electrolytes were normal. Liver chemical tests showed the icteric index to be 8; alkaline phosphatase, 5.0; total protein, 5.6 gm.%; albumin-globulin ratio, 2.9/2.7; cholesterol-esters, 139/56; prothrombin time, 19 sec. (17 sec. control). Reticulocyte count was less than 1%. The patient showed no response to tuberculin of various strengths down to 1/1000.

Chest x-ray showed a large pleural effusion on the left.

Treatment and Course: Thoracentesis yielded 2,500 ml. yellow clear fluid with a specific gravity of 1.020, in which were found 3,600 red blood cells and 200 lymphocytes/mm^3. Total protein was 4.6 gm.% and sugar 64 mg.%. After removal of the pleural effusion an x-ray showed a bronchopneumonic process in the left lower lobe, with cavity formation and honeycombing. Specimens of blood, pleural fluid, sputum and gastric contents were obtained repeatedly for bacteriologic study. A concentrated sputum smear was negative for acid-fast bacilli. The patient was hydrated and fed intravenously. He received blood and was started on oral iron and tetracycline pending culture results. No improvement followed. Bronchoscopy was performed. Creamy pus was seen oozing from the orifice of the bronchus leading to the superior segment of the left lower lobe. Erythromycin was added after *Staphylococcus aureus* coagulase-positive was cultured from the bronchial aspirate.

However, the patient remained febrile with spiking temperatures, and continued to deteriorate. The white blood cell count and the hematocrit showed a slow rise after repeated blood transfusions and parenteral iron. Tube feeding was instituted. On August 15 tetracycline was replaced by Chloromycetin, without effect.

X-rays and the clinical course became more suggestive of underlying pulmonary tuberculosis. Despite consistently negative smears, cultures and tuberculin-sensitivity reactions, isonicotinic acid, 300 mg., and PAS, 15 gm. daily, were started on August

19. On August 24 the temperature dropped to subnormal levels, while the blood pressure fell to 60/40 mm. of Hg. Again whole blood was given, with only a transient effect on the blood pressure. In Trendelenburg position the blood pressure was barely maintained above shock levels. The patient responded weakly to painful stimuli. On August 26 the patient appeared moribund. One hundred milligrams of cortisone were given intravenously and this dose was continued daily. In the following days the blood pressure became stable, the temperature rose to normal, and the patient began to respond to verbal stimuli and moved around in bed. After two weeks he started to eat by himself. The temperature remained normal. After three weeks he was able to sit in a wheelchair. He became an alert and contented, albeit euphoric, member of the ward. Serial x-rays of the chest showed no significant change. More than three months after admission, cultures positive for acid-fast bacilli were obtained. On the forty-fifth day of cortisone treatment (October 10) a gradual reduction of the dose was begun. On November 25 all steroid therapy was discontinued. At no time was a recurrence of fever, anorexia or malaise noted in the following month of observation. It is interesting that a repeated tuberculin-sensitivity test (PPD second strength) was positive on November 11, that is, while the patient received cortisone. He received a total of 1,500 mg. of cortisone or hydrocortisone over a period of 31 days.

Case 3. A 67 year old Negro woman was admitted to another hospital on February 20, 1956, with a two-week history of weight loss, weakness and fever. A chest x-ray showed massive bilateral disease. Sputum was found to be positive for acid-fast bacilli, and the patient was started on isoniazid, 300 mg., and streptomycin, 1 gm. daily.

Because of progressive confusion, disorientation and delusions she was transferred to Bellevue Hospital (psychiatric medical ward) on February 23, 1956. Little additional history was obtained. It was learned later that the patient had drunk considerably for many years, but there had been no significant previous illness.

The physical examination on admission showed an emaciated, severely, acutely, and chronically ill woman who coughed occasionally without producing any sputum. The pertinent positive and negative findings were: temperature, 102° F.; pulse, 120; blood pressure, 110/80 mm. of Hg; respiration, 22. The fundi were unremarkable. The neck was moderately rigid. The chest expanded poorly; there was no obvious asymmetry. There was dullness to percussion over the right upper lung field anteriorly. In this area there was bronchial breathing and many fine râles were heard. There was extensive sacral decubitus. Examination of heart, abdomen, bones and joints and nervous system was unremarkable.

Laboratory findings on admission showed a normal urine analysis. Hemoglobin was 11.5 gm.%; white blood cell count was 6,400, with 83% segmented cells, 10% monocytes and 7% lymphocytes. The patient produced no sputum. Cerebrospinal fluid was normal. Mazzini test was negative. Specimens of gastric aspiration, urine and cerebrospinal fluid were sent for culture repeatedly. X-ray on admission showed massive bilateral pulmonary opacities, more marked on the right, with no evidence of cavitation or pleural effusion.

Treatment and Course: The patient was catheterized because of incontinence. Hydration and feeding had to be instituted intravenously and by gastric tube. Streptomycin, 1 gm., and isoniazid, 300 mg. daily, were continued. On this regimen the patient became gradually worse, the temperature showed a hectic course, and on March 5, 1956 she appeared moribund. She was unresponsive to any but painful stimuli and was markedly hypotensive.

Intravenous hydrocortisone, 50 mg. four times a day, was instituted. In the following days the patient started to answer questions, to move about in bed and to take fluids by mouth when helped, and the temperature leveled off to normal.

On March 17, that is, 13 days after steroid therapy had been started, the cortisone dose was reduced to 50 mg. twice a day. On March 12 the patient was able to eat by herself. On March 19 she sat in a wheelchair for the first time.

Because of a sudden spiking fever due to several abscesses around the area of decubitus, and because of her otherwise stabilized clinical condition, cortisone was discontinued on March 23. Forty units of ACTH gel were given on March 25 and 20 units on March 29. The patient received a total of 3.2 gm. of cortisone and 60 units of ACTH in the course of 21 days.

Drainage of the abscesses, in combination with antibiotic therapy, was followed by a normal temperature and rapid healing of the severe decubitus. By the end of April the patient was up and about. The serial chest films continued to show remarkable clearing of the infiltrate on both sides. At no time was there definite radiologic evidence of cavitation.

It is interesting that the tuberculin test done during cortisone treatment (PPD, first and second strength) remained negative in this instance. On September 22 O. T. 1:10,000 was positive.

It may be pointed out that the radiologic improvement preceded the use of broad-spectrum antibiotics, and that bacteriologic studies were then negative. Two gastric aspirates proved positive for acid-fast bacilli. There was sensitivity to all three drugs.

Serial urines, two cerebrospinal fluid specimens and subsequent gastric aspirates have remained negative. At no time has evidence of "rebound" been observed.

Discussion

All three patients were severe chronic alcoholics, who are known to have little resistance to infection in general. The three cases presented had several features in common which led to the decision to use steroid hormones:

1. They had far advanced pulmonary tuberculosis which had never been treated prior to the described admission.
2. There was rapidly progressive deterioration, clinically characterized by severe toxicity (high fever or subnormal temperatures, semicoma or delirium and shock), in addition to respiratory distress and cyanosis caused by the local process.
3. They showed no response to vigorous antituberculosis chemotherapy before steroid therapy was initiated.

The daily dose of steroids used did not exceed 200 mg. of cortisone, given either intravenously or orally. Withdrawal of steroid therapy was started by slowly decreasing doses as soon as the patients were able to sit in a wheelchair and seemed to be adequately stabilized, as indicated by temperature, blood pressure, mental status and subjective well being. No rebound phenomena were observed, and all three patients continued their improvement after cessation of hormone therapy. Cases 1 and 2 showed no significant change in their x-ray picture; case 3 exhibited a striking clearing of the pulmonary lesions. The sputum remained positive during the period of observation in our three patients. All three showed a favorable response to the addition of steroid hormones to vigorous antituberculosis chemotherapy, as has been described by others.

Patients with rapidly progressing pulmonary tuberculosis with a fulminating clinical course have responded well to steroid treatment, according to several observers, and there is an increasing number of phthisiologists who have become convinced of the lack of evidence that steroid hormones enhance dissemination and spread in the presence of adequate antibiotic coverage.[13, 14, 17, 18, 22, 29, 31, 32] A distinction must be made between the striking symptomatic improvement (fever, appetite, weight, subjective well-being) described in most reports, and the amelioration of the tuberculous process itself, as evidenced by x-rays, sputa and other laboratory information regarding activity. As far as the latter is concerned there is less agreement, and only a few case reports [14, 15, 16, 20, 31, 32] are available which indicate that the improvement was more than symptomatic.

It has been suggested that patients who died during combined treatment may have been caught too late, when destructive processes had become too extensive. Their course seemed not to be accelerated but rather prolonged.[19, 32] Patients invariably responded poorly to steroid hormones when they had been treated with streptomycin, PAS and isonicotinic acid for extensive periods and had become resistant to these drugs. The disease progressed, again without acceleration and without evidence (x-ray or autopsy) of dissemination.[13, 15, 19]

There is no unanimity among advocates of combined treatment regarding the duration of steroid therapy. Some feel that treatment should be continued for many months.[16, 19] This point of view is based partly upon the observation that severe recurrences (fever, "toxicity," anorexia) were not uncommon when an attempt was made to withdraw the steroids. Others advise interruption of the course whenever the severe toxicity which prompted the use of steroid hormones has abated.[13, 20, 31, 32]

The dosages used vary considerably but tend to be moderate, that is, if ACTH was employed, usually not more than 50 units, and when cortisone and related drugs were chosen, not more than 200 mg. per day were administered. The difference between a beneficial effect and a deleterious result of hormonal therapy may lie in the amount of hormone administered, and the importance of a cautious dosage schedule has recently been restated.[31, 32]

Most authors seem in agreement that combined treatment should be reserved for the very seriously ill patient in whom antibiotic therapy alone does not prevent further deterioration.[15, 20] However, others suggest that ACTH or cortisone may be beneficial in early tuberculosis, for instance, in acute pleural effusions, as it seems to enhance the effect of the antituberculosis drugs [12, 14, 16, 17] and to prevent adhesion formation.[31, 32]

Conclusion

The three cases presented seem to support the contention, expressed with increasing frequency in the literature, that steroids may have a place

in the treatment of pulmonary tuberculosis, provided the indications and contraindications which have been reviewed are taken into account. It cannot be stated at this time whether more than symptomatic improvement has been achieved. However, this improvement may form a bridge over a desperate danger zone in the course of the disease.

Summary

The use of ACTH and cortisone in combination with antibiotic drugs for the treatment of overwhelming bacterial infections has become an accepted practice. In the treatment of pulmonary tuberculosis, however, such combined therapy has been barred until recently, because of reports of acceleration and dissemination of the tuberculous process following ACTH or cortisone administration.

It is pointed out that much of the fear of the use of steroids in the presence of active tuberculosis was based upon animal experiments performed under conditions which are not comparable to clinical situations.

From the literature it is evident that bad experiences were mostly attributable to resistance to antituberculosis drugs or to administration of steroids without antibiotic coverage. There is an increasing number of reports, mostly from French and English sources, of beneficial results obtained from combined therapy in pulmonary tuberculosis.

Three patients are presented, all chronic alcoholics with far advanced pulmonary tuberculosis, who became moribund while on antituberculosis therapy and who improved dramatically following the institution of steroid therapy. The improvement was manifested by elevation of blood pressure, reduction of temperature, and increase in mental alertness and in subjective well-being, ability to take oral feedings and to tolerate mobilization. In two cases the chest x-ray did not significantly change during 31 days of cortisone treatment. In one case there was striking clearing of massive infiltration. In none was there evidence of spread or dissemination. The daily dose of cortisone (given intravenously during the first days of therapy, intramuscularly thereafter) did not exceed 200 mg. in one, and 100 mg. in two patients. With stabilization of the clinical condition the dose was slowly decreased, without evidence of "rebound." The three patients continued their improvement after cessation of steroid administration.

These three cases support the evidence in the literature that advanced active pulmonary tuberculosis, especially in debilitated persons, responds well to combined therapy, provided adequate antibiotic coverage is instituted and drug resistance is excluded.

No opinion can be expressed as to whether hormone therapy causes only symptomatic improvement, or whether the tuberculous process itself can be influenced, either by direct action of the hormones or by enhancing the effect of antibiotics.

SUMMARIO IN INTERLINGUA

Le uso de ACTH e cortisona in combination con antibioticos in le tractamento de pervagante infectiones bacterial ha devenite un practica acceptate. Tamen, in le tractamento de tuberculose pulmonal, ille therapia combinate ha essite rejicite usque al passato recente a causa de reportos de acceleration e dissemination del processo tuberculotic post administrationes de ACTH o cortisona.

Es signalate que le objectiones contra le uso de steroides in le presentia de tuberculose active es basate in alte mesura super constatationes in experimentos animal que esseva executate sub conditiones non comparabile con le situation clinic.

Le studio del litteratura rende evidente que le majoritate del experientias adverse esseva attribuibile a refractorietate contra drogas antituberculotic o al administration de steroides sin protection antibiotic. Il existe, del altere latere, reportos de origine predominantemente francese e britannic e de frequentia crescente que resultatos benefic esseva obtenite per le uso de therapias combinate in casos de tuberculose pulmonar.

Es presentate tres patientes, omnes alcoholicos chronic con avantiatissime tuberculose pulmonar, qui deveniva moribunde durante lor tractamento per un therapia antituberculotic e qui se meliorava sensationalmente post le institution de un therapia a steroides. Iste melioration esseva manifeste in elevation del pression sanguinee, reduction del temperatura, augmento del alertia mental e del ben-esser subjective, e le retorno del capacitate de acceptar nutrimento oral e de tolerar mobilisation. In duo casos, le roentgenogrammas thoracic non monstrava alterationes significative durante le 32 dies del curso de cortisona. In le tertie caso il habeva un frappante clarification de infiltrationes massive. Nulle del tres casos revelava signos de extension o dissemination. Le dose diurne de cortisona (administrate per via intravenose durante le prime dies del therapia e per via intramuscular durante le resto del curso) non excedeva 200 mg in un del patientes e 100 mg in le duo alteres. Post stabilisation del condition clinic le dose esseva reducite lentemente, e isto non resultava in signos de "resurgentia." Le tres patientes continuava progreder post cessation del administration de steroide.

Iste tres casos supporta le indicationes in le litteratura que active tuberculose pulmonar in stato avantiate, specialmente in personas debilitate, responde ben al therapia combinate, providite que un adequate protection antibiotic ha essite effectuate e que le caso non es un caso de resistentia al droga usate.

Le presente articulo non responde al question si le therapia hormonal causa solmente un melioration symptomatic o si illo pote influentiar le processo tuberculotic mesme, sia per un action directe o sia per promover le effecto del antibioticos.

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FAT EMBOLISM: A PROBLEM OF INCREASING IMPORTANCE TO THE ORTHOPEDIST AND THE INTERNIST *

By JULIAN LOVE, M.D., F.A.C.P., *Duarte, California,* and WILLIAM S. STRYKER, M.D., A.A.O.S., *Corona, California*

THE rapid advances of this modern era, which have improved living conditions for the masses, plus the advent of antibiotics, have brought about remarkable changes in the pattern of morbidity. This has been a mixed blessing for, although noneffectiveness and fatality due to infections and contagious diseases have been reduced markedly, this has been countered by an increase in trauma with the automobile as the principal agent.

With the numbers of cars sold ever mounting (over 7 million in 1955), their speeds and horsepower steadily climbing, their drivers so often youths or inebriates of erroneous judgment, or the elderly with slower reaction times, there can be little doubt that treatment of traumatic injuries and their complications will occupy a progressively larger share of almost every physician's time. Accordingly, the internist must become acquainted with clinical syndromes that complicate injury states, especially those that simulate internal diseases, so that he, when serving as a consultant, may make the diagnosis and authoritatively proffer advice concerning the management of such problems.

Fat embolism secondary to traumatic injuries, although described long ago, is a classic example of the newer morbidity. On the Orthopedic Service of the U. S. Naval Hospital, Corona, California, it was the cause of grave concern in eight patients, two of whom died, and an incidental finding in at least 10 others in a period of four years.

It is our purpose in this paper to discuss the incidence of post-traumatic fat embolism, to describe its etiology and pathophysiology, to delineate the clinical picture when fat embolization is of sufficient extent to be clinically significant, and, finally, to propose a few therapeutic measures based upon studies of others as well as our own experiences.

ETIOLOGY AND PATHOPHYSIOLOGY

The origin of the embolic fat has not been determined with finality even in cases of severe trauma. The most likely source is the fatty marrow of a fractured adult long bone. Several authors [1-7] have reported cases of massive bone marrow embolism following trauma, and this is sufficient to prove

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Requests for reprints should be addressed to Julian Love, M.D., City of Hope National Medical Center, Duarte, California.

that marrow and, by analogy, the marrow fat of the long bone, can be a source of significant embolization. Glas et al.[4] have demonstrated that the quantity of fat removed from the marrow of the femur of one rabbit, if injected into the ear vein of another, was sufficient to kill nine out of 10 of the recipient animals. They have shown that less than half of the fat contained in the femur can cause fatal fat embolism. They have fractured femurs whose fat content had previously been stained and have demonstrated that fat emboli appear in the pulmonary circulation within seconds after injury.

Proceeding on the assumption that the emboli are derived from the bone marrow, Gauss[5] and, later, others[6-7] pointed out that three conditions are required for the production of fat emboli:

1. The envelope of the fat cell must be ruptured and liquid fat freed.
2. Veins in the vicinity must be torn.
3. Increased pressure must be present to force the fat into the torn veins.

These conditions are met by the trauma which fractures an adult long bone and are intensified by the churning of the fracture site from prolonged transportation and/or inadequate splinting. Warren[6] warned that "any mobilization of the fracture site after local swelling has occurred is fraught with hazard as a considerable degree of tissue pressure then exists. Disturbance of the region may then dislodge the fibrin clot occluding the disrupted veins opening them to the free fat present."

The anatomy of the medullary canal is well suited to the entrance of large fat globules into the venous circulation. Schaffer,[8] in a microscopic study, found that the marrow capillaries are large (about 25 micra, in contrast to the capillaries elsewhere in the body, which are about 10 micra), and that these capillaries emptied into wide venous sinusoids that were extremely thin-walled. It is not difficult to imagine that these fragile sinusoids, as well as the thin walls of the fat cells, are easily ruptured by either the fracture or the jarring of the entire skeleton that occurs in the high velocity impacts of automobile accidents. When the released fat particles reach the circulation they assume a globular shape due to surface tension (figure 1). Arriving at the smaller (10 micra) capillaries of the pulmonary circulation, they became arrested, temporarily interfering with the gaseous diffusion functions of the alveolar circulation. This obstruction to gaseous exchange is abetted by edema and hemorrhage into the alveoli themselves. Anoxic hypoxemia and hypercapnia ensue and cause cyanosis and hyperpnea. These respiratory changes may be responsible in part for the cerebral signs of restlessness and delirium. In time, pressure in the pulmonary circulation elongates the pliable fat droplets (figure 2), forcing them to pass through into the venules and pulmonary veins and into the systemic circulation, whence the emboli are again arrested in terminal capillaries. The organs

and structures supplied by systemic capillaries then become victims of this embolization process. The one organ most immediately susceptible to interference with its oxygen supply is the brain, and cerebral symptoms such as delirium and coma appear.

In fatal cases the kidney glomeruli are found to be extensively occluded; however, there are sufficient patent channels in the glomerular tufts so that

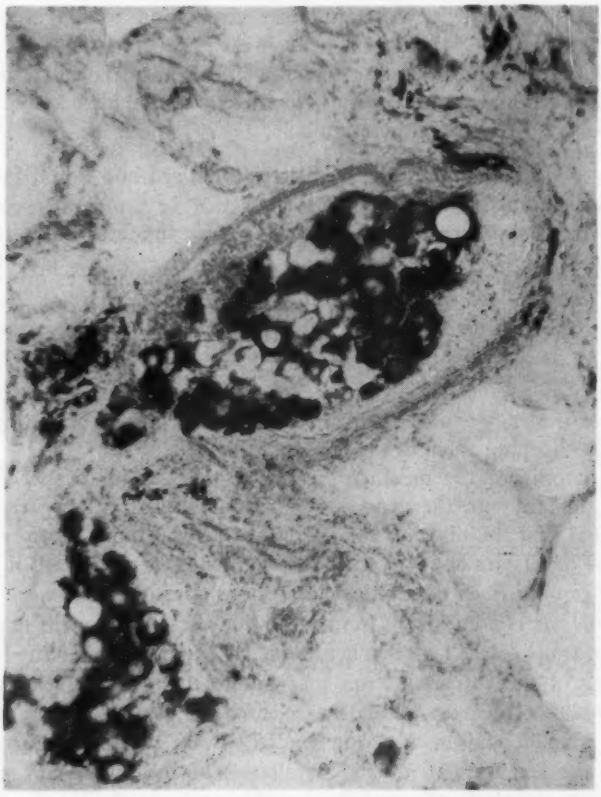


FIG. 1. Fatty emboli in pulmonary vessel from a patient with post-traumatic fat embolism. Stained with Sudan III. Note globular shape of fatty particles within the vessel. (Courtesy of Dr. B. E. Konwaler.)

signs of renal failure are not present and abnormal findings in the urine are minimal, if they are present at all. In recovered cases there is no evidence of impaired renal function as shown by the kidney's ability to concentrate. During the acute phase, fat globules will be found in the urine in direct relation to the diligence with which they are sought. It must be remembered that they float on the surface of the urine, as pointed out by Scuderi,[9]

and that they may be retained in the bladder unless it is completely emptied. Concurrently, emboli lodge in the skin as well, but physical evidence of them does not appear as early as the cerebral or pulmonary manifestations. The tiny petechiae produced by them are usually seen about the third day. They have a curious predilection for the upper torso, particularly the lateral aspects of the thorax and the axillae (figure 3).

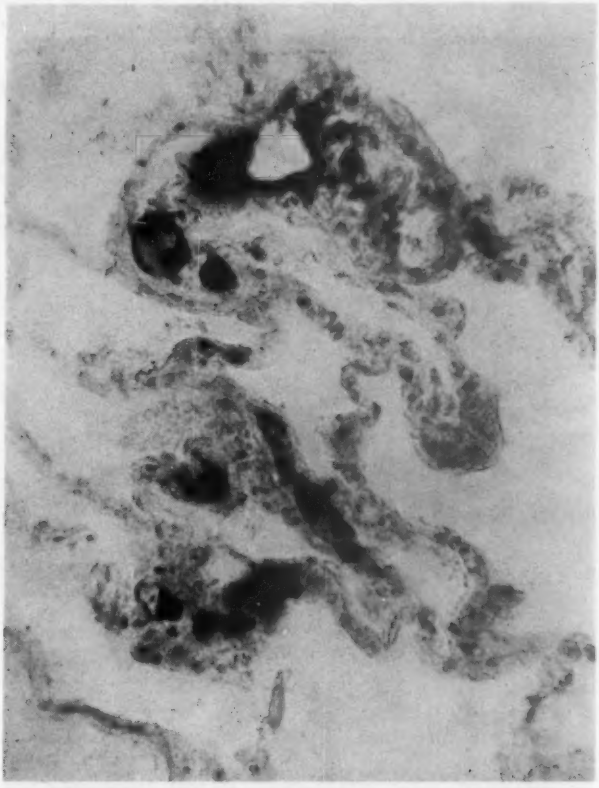


FIG. 2. Fat emboli in vessels of alveolar walls. Note flattening out and elongation of emboli. Stained with Sudan III. (Courtesy of Dr. Benjamin E. Konwaler.)

TYPICAL CLINICAL PICTURE

The clinical findings are quite characteristic. The patient is usually the victim of severe trauma from sudden deceleration, crushing or a burn, and usually there is a fracture of a major long bone, such as the femur or tibia.

He usually displays a "free interval" following the injury (although, needless to say, it can occur in an individual who has a concomitant cranio-

cerebral injury with unconsciousness). Then the nail-beds and lips become cyanotic, frequently very deeply so, and the respiratory rate and depth increase. In some cases the rate exceeds 50/min. and the respirations are of a stertorous, dyspneic quality. There are restlessness and anxiety, which may progress to delirium and then coma.

On the second to third day fine brownish petechiae—often only 1 mm. in diameter and frequently overlooked as normal skin pigmentations—



FIG. 3. Showing the characteristic distribution of the petechiae in the axillary region.

appear over the upper trunk, especially in the axillae and the lateral aspect of the chest.[10] This odd predilection of the petechiae of fat embolism to locate in the upper torso has been noted by several authors, but no satisfactory explanation for this phenomenon has been offered. Nevertheless, it serves as a valuable diagnostic feature. Many authors have stressed the presence of petechiae in the conjunctivae and in the eyegrounds, but this is not in accord with our observations.

Differential Diagnosis

The differential diagnosis is not difficult in the full-blown case with both pulmonary and cerebral signs. When the latter predominate it may be difficult to differentiate from intracranial bleeding, especially if there is a relatively free interval followed by progressively deepening coma. In fat embolism there may be many and bizarre neurologic findings, such as muscular twitching and even convulsions, but, due to its diffuse nature, there are no localizing or lateralizing signs. The two processes could well coexist, since they are usually the result of severe trauma. If there is any reasonable doubt, exploratory burr openings should be made in the parietal region *bilaterally*. These are made under local anesthesia in a few minutes with very minimal risk.

Fat embolism seems to have a special predilection for the alcoholic, and the early cerebral signs of restlessness followed by delirium must be differentiated from delirium tremens. A diagnostic-therapeutic trial of promazine or chlorpromazine may help in this distinction.

The cardiorespiratory signs may be confused with those of cardiac contusion. In both there may be dyspnea and precordial distress, but in our experience in cardiac contusion there has not been the rapid, deep respiration with cyanosis, and the cerebral signs do not progress beyond restlessness and anxiety. The electrocardiogram is usually decisive. In cases of fat embolism, electrocardiograms are essentially normal. In cases of cardiac contusion there is electrographic evidence of myocardial injury, with elevations of the S-T segment and T wave inversion.

The shock syndrome must be considered in the differential diagnosis. We are convinced that many of the cases of delayed shock that do not respond to blood replacement are in reality fat embolism and should be treated as such.

The question of a pulmonary embolus from an intravascular clot may be raised, but there is little trouble in its differentiation. Symptoms of fat embolism are seen within the first one to six days after injury; pulmonary embolism, rarely before the tenth.

Treatment

Treatment is of definite benefit. The best is preventive. The majority of our cases have been transported for relatively long distances with inadequate—if any—splintage of fractures. Despite the training that has been given by Red Cross Units, the Armed Forces, the Boy Scouts and other groups, only a small minority of the fractures that we receive are effectively splinted. Correct splinting, careful transportation and early definitive reduction and immobilization of fractures should be of help.

If restlessness and cyanosis occur in the presence of an adequate blood pressure and hematocrit, oxygen should be given, preferably under pressure. We have found it to be our most beneficial single agent.

Herrmann [11] has shown that alcohol results in a clearing of the patchy infiltration in the lungs of animals in which emboli have been produced by intravenous injections of fat. We have been using a 5% glucose–5% alcohol mixture as a semi-routine procedure when fluids are required in our cases of severe trauma, and there have been no recent cases of clinically significant fat embolism. We employ a low fat diet for those able to take food, on the theory that the body should be able to dispose of the fat emboli more readily if the channels are not loaded with normal metabolites. Heparin in daily doses of 25 mg., insufficient to disturb coagulation, is recommended because of its indirect lipolytic effect.

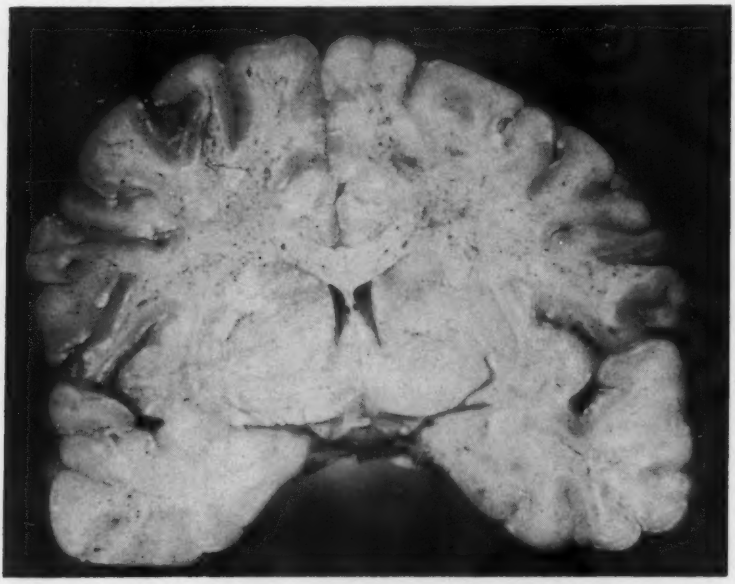


FIG. 4. Fat emboli in brain and cerebellum from a case of post-traumatic fatty embolism. Note predilection for white matter.

Of the patients with fat embolism of clinical significance the following two have been selected for illustration of the clinical features previously described.

CASE REPORTS

Case 1. A 20 year old sailor sustained severe injuries, including fractures of the left femur and tibia, in an automobile accident on August 7, 1952. He was carried a distance of 83 miles but the injured extremity was not splinted. His injured lower extremity was then splinted, and he was transported an additional 100 miles to the U. S. Naval Hospital, Corona, California, arriving eight and one-half hours after the accident.

On admission he displayed a pallor of his face and nail-beds. His blood pressure was 90/60 mm. of Hg; pulse, 108. He answered questions lucidly. There were

dirty lacerations over the left knee and left leg, and obvious fractures, noncommunicating in type, of the left femur and tibia. His lungs were resonant, and his breath sounds were normal throughout.

Initial treatment consisted of wound excision and closure under Pentothal-nitrous oxide-oxygen anesthesia, and the institution of balanced traction for his fractures. Following this he became cyanotic. Nasal oxygen at the rate of 6 L. per minute was begun. During the night his respirations increased progressively to 30 per minute, and he became quite restless. Dullness developed in the base of his right lung, with râles superior to this. Twenty-eight hours after his accident he became

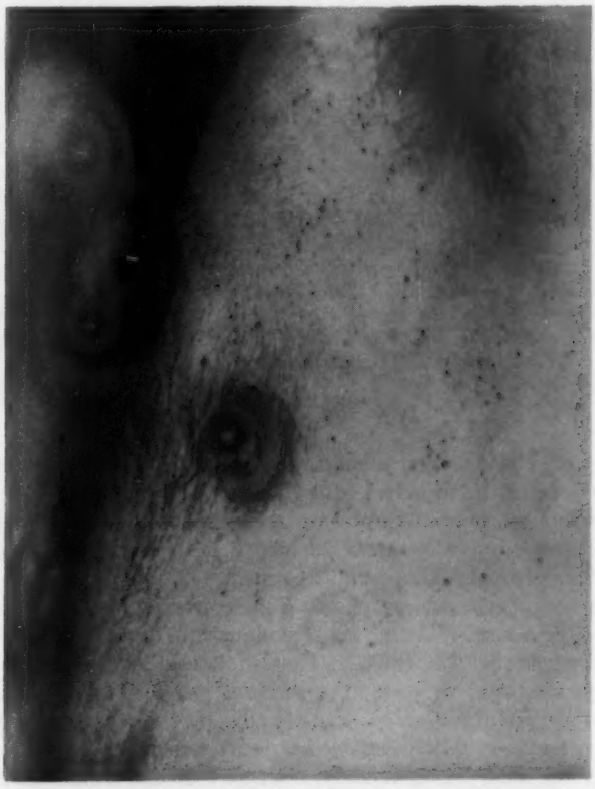


FIG. 5. Petechial skin manifestations of fatty embolism in axillary region. Patient recovered.

semiconscious and incontinent of urine. Three hours later he was comatose, his respirations were 48 per minute, and his nail-beds were very cyanotic. The possibility of intracranial hemorrhage was considered, but exploratory trephining was not performed because of the absence of neurologic findings other than coma.

His condition steadily worsened. Despite nasal oxygen therapy he remained cyanotic and his respirations increased to 70 per minute. Moist râles were prominent throughout both lung fields. He died 62 hours following his injury.

At post mortem the lungs were markedly firm and deep purple in color. When they were sectioned the surface was wet and markedly congested, and there was

frothy fluid in the bronchi. There were numerous petechiae over the epicardium. Externally the brain appeared normal, but serial sections showed myriads of petechiae throughout the white matter (figure 4). Frozen sections of the brain and lungs stained with fat stains revealed very extensive occlusion of the capillaries by fat emboli.

Case 2. A 34 year old officer sustained multiple injuries in an automobile accident on February 21, 1955. These included a compound fracture of the mid-diaphysis of the right tibia and fibula, associated with marked swelling and external marks indicating that this was the result of a crushing injury. He was not rendered unconscious.

He was placed on a litter without any splinting whatsoever and transferred to the U. S. Naval Hospital, Corona, California, a distance of about 40 miles. He arrived one and a half hours after the accident in profound shock, with no detectable peripheral pulse or blood pressure.

Anti-shock measures were instituted and the fracture of the right leg was treated by traction on a Böhler frame. On the second day his blood pressure stabilized at 130/80 mm. of Hg, and his hematocrit was 36. He was lucid.

About 36 hours after the accident he became quite restless and then disoriented, requiring paraldehyde for sedation. His respirations were deep and labored, and there was cyanosis of the nail-beds. Disorientation alternating with periods of relative lucidity continued for the next 14 days, with gradual clearing of his sensorium. Forty-eight hours after his injury petechiae were present in the axillary and antero-lateral chest areas, and these were still prominent seven days later.

He achieved an excellent degree of recovery, returning on November 8, 1955, to his position as a Public Relations Officer, fully ambulatory in a long leg brace to protect his healing tibial fracture. There was no demonstrable evidence of residual brain damage.

Summary

1. Under the fast-moving conditions of modern life, trauma is displacing infection as one of the principal causes of morbidity. One of its complications, fat embolism, presents problems in differential diagnosis and management wherein the internist can be of help if he is cognizant of the clinical findings, their pathophysiology and treatment.

2. The typical case occurs following the fracture of a long bone, usually the tibia or the femur. There is a "free interval" during which the patient is lucid and relatively comfortable. This is followed by the pulmonary phase, with its cyanosis and dyspnea; the cerebral phase, with restlessness, disorientation, delirium and coma; and, finally, by the cutaneous phase, with its typical petechiae. The petechiae are found principally in the axillae and pectoral regions and, less commonly, elsewhere on the trunk, the neck, conjunctivae and, rarely, in the ocular fundi. The petechiae are frequently as small as 1 mm. in diameter and are easily confused with normal skin pigmentations.

3. Treatment is of definite benefit. The injured should be transported as little as possible, their fractures should be carefully splinted, and they should not be jostled in a speeding ambulance. Fractures should be reduced and immobilized as soon as consistent with the general condition. Intravenous fluids for the first few days should consist of 5% glucose–5% alcohol

for its emulsifying action. If pulmonary or cerebral signs of fat embolism develop, oxygen, preferably under pressure using a Bennett respirator, should be used. Twenty-five milligrams of heparin daily are suggested, for their activating effect on lipoprotein lipase. Two illustrative cases are presented.

SUMMARIO IN INTERLINGUA

Sub le conditiones del civilisation moderne, trauma reimplacia infection in su rolo de un del principal causes de morbiditate. Un del complicationes de trauma, le embolia de grassia, presenta problemas in le diagnose differential e in le tractamento que le internista pote reducer si ille cognosce le pertinente constatationes clinic, le pathophysiologia del phenomeno, e su tractamento.

Le caso typic de embolia grasse occurre post fractura de un osso longe, usualmente le tibia o le femore. Il ha un "intervallo libere" durante le qual le patiente es lucide e relativemente comfortabile. Isto es sequite per un phase pulmonar con cyanose e dyspnea, un phase cerebral con signos de agitation associate con disorientation e delirio e coma, e finalmente le phase cutanee con typic petechias. Le petechias occurre principalmente in le axillas e le regiones pectoral e, minus communmente, in altere partes del trunco, le collo, le conjunctivas, e rarmente in le fundo ocular. Le petechias ha frequentemente diametros de non plus que 1 mm e es facile a confunder con normal pigmentation del pelle.

Tractamento del condition es clarmente benefic. Le vulneratos deberea esser transportate le minus possibile. Lor fracturas deberea esser cautemente fixate, e illes non debe esser chocheate in un ambulantia a carriera rapide. Le fracturas deberea esser reducite e immobilisate le plus promptemente compatibile con le condition general del subjecto. Fluidos intravenose durante le prime dies deberea consister de glucosa a 5% con 5% de alcohol (a causa de su effecto emulsive). Si symptomas pulmonar o cerebral de embolia de grassia se disveloppa, oxygeno debe esser administrate—preferibilemente sub pression per medio de un respirator Bennett. Es presentate duo casos illustrative.

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USE AND ABUSE OF ANTICHOLINERGIC DRUGS IN THE MANAGEMENT OF GASTRO-INTESTINAL DISEASE*

By ALVIN J. CUMMINS, M.D., *Memphis, Tennessee*

"ANTISPASMODIC" drugs, as applied to the gastrointestinal tract, are of two varieties: (a) those depressing smooth muscle activity directly, and (b) those acting through inhibition of the parasympathetic nervous system. The first type, as exemplified by papaverine and the nitrites, has rather evanescent effects on muscle activity and, because of lack of effect on gastric secretory function, has found relatively little application in gastroenterologic therapeutics outside of acute exhibition in cases involving spasm of the biliary system. The second type of drug action can be effected either through depression of the central nervous system, blockade of peripheral ganglionic transmission or by inhibition of postganglionic parasympathetic impulses. Central depressant drugs produce mental and mood changes as side-effects, and their "antispasmodic" action, in nonhypnotic doses, is minimal. Ganglionic blocking agents, such as tetraethylammonium and hexamethonium, are of little practical use because they also block sympathetic transmission and lead to widespread undesirable side-effects. The most useful "antispasmodic" drugs in gastroenterology are the postganglionic parasympathetic inhibitors, or "anticholinergic" drugs. These act by preventing the response of end organs (such as gastric secretory glands and intestinal smooth muscle) to parasympathetic cholinergic stimulation. It is essential, however, to stress that certain of these agents also possess the ability to inhibit (to a certain degree, at least) ganglionic transmission as well, and may thus interfere with the sympathetic as well as the parasympathetic system. Such ganglionic action has been demonstrated for methantheline and propantheline bromide, oxyphenonium, tricyclamol, and probably for atropine as well.

Numerous anticholinergic drugs are currently on the market and new ones are constantly being introduced. Because of the prevalence of gastrointestinal disorders in clinical practice and the paucity of specific therapies, use of such drugs is widespread, and it behooves the physician to be thoroughly acquainted with their applications and limitations. The purpose of this communication is to review briefly, in a general way, some of the principal uses of anticholinergic drugs in the management of gastrointestinal disorders, and especially to emphasize their contraindications and limita-

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From the Department of Medicine, University of Tennessee College of Medicine, Memphis, Tennessee.

Requests for reprints should be addressed to Alvin J. Cummins, M.D., Assistant Professor, Division of Medicine, The University of Tennessee, Memphis 3, Tennessee.

tions. No attempt will be made to assess the relative efficacy of the currently available drugs or to give specific details of their use.

A. *Some Useful Applications.*

1. *Peptic ulcer disease:* Among the physiologic derangements of duodenal ulcer are increased gastric secretion and enhanced or deranged pyloroduodenal motility. Gastric ulcer, though associated with normal or decreased gastric secretion, heals well when acidity is reduced. The mechanism of ulcer pain is still not well understood but seems related either to acidity [1] or abnormal motility,[2] or both.[3] Effective doses of potent anticholinergic drugs depress the cephalic (vagal) phase of gastric secretion and thus facilitate ulcer healing. In addition, motility is inhibited, and this alone, or possibly in combination with the secretory depression, often leads to prompt relief of ulcer pain.[2] The physician must not be lulled by this clinical response into a false sense of security, but should persist with drug therapy and, in addition, be certain his patient is receiving the proved benefits of other portions of the anti-ulcer régime, such as frequent-feeding bland diet, sedation, psychotherapy, etc. Anticholinergic drugs benefit the ulcer patient not only as indicated above but also by slowing the rate of gastric emptying, thus permitting ingested food and antacids to remain longer in contact with the acid gastric secretion and exert more effectively their neutralizing action.

The main emphasis in the medical treatment of marginal or jejunal ulcer following subtotal gastrectomy should be on anticholinergic drugs. In this instance, food and antacids often dump rapidly out of the gastric remnant through the stoma, providing little neutralizing effect. Depression of secretion therefore remains the principal therapeutic weapon.

The physician should be aware of the fact that he accomplishes only a reduction of the vagal phase of gastric secretion with anticholinergic drugs, and that the hormonal phases (gastric and intestinal) are not interfered with. He should continue to rely heavily on the other staples of therapy in his complete management of the ulcer patient.

2. *Functional indigestion and gastritis:* Included in these terms is a multitude of clinical syndromes, some rather ill defined, which are among the most common conditions faced by the doctor. Though pathophysiologic mechanisms here are but poorly understood, it is known that abnormal gastroduodenal motility and excess gastric secretion are accompaniments, if not originators, of much of the symptomatology.[4] If there is reason to suspect the presence of such secretory-motor disturbances, anticholinergic drugs can be expected to aid in management. Their results are sometimes rather dramatic when properly combined with dietotherapy, sedation, psychotherapy and elimination of specific etiologies, if discovered.

3. *Pancreatitis:* Medical management has now largely superseded surgery in dealing with the patient with uncomplicated acute pancreatitis. A

most important part of this management concerns institution of "physiologic rest" for the diseased pancreas.[5] It is reasonably clear that vagal influence on pancreatic function includes: (a) stimulation of secretion through the release of the hormone secretin from the intestinal mucosa by the action of gastric acid; (b) a direct stimulating effect on pancreatic secretion by action on the acinar cells; (c) an excitor influence on contraction of the walls of the larger pancreatic ducts, and (d) a possible increase in pancreatic blood flow.[6] Effective block of all of these effects of vagal activity would appear indicated in a pancreatic "rest" program, and much reliance is placed currently on accomplishing this with anticholinergic drugs. The evidence seems to indicate that the desired result can be attained, to some degree at least, by physiologic doses of such drugs.[7, 8, 9] Most benefit probably derives from block of the hormonal mechanism of pancreatic secretion by decrease in gastric acid production. Once again it must be emphasized that reliance on anticholinergic drugs must not be made to the point of neglecting other equally or more important aspects of therapy, such as gastric suction, fluid and electrolyte therapy, antishock measures, antibiotics, etc.

In the treatment of chronic pancreatitis with relapsing episodes of pain, anticholinergic drugs should be employed for the same rationale as given above. Results of medical management here, however, are frequently disappointing, probably because of the attendant disturbances resulting from chronic structural damage of the pancreas.

4. *Dumping syndrome:* A not infrequent effect of subtotal or total gastrectomy, the dumping syndrome results, at least in part, from mechanical distention of the small intestine as a result of release into it of postprandial hypertonic contents of the gastric remnant. Empirically, the administration of anticholinergic drugs has been found to ameliorate or relieve completely the distressing symptoms in some, but not all, cases. Their trial in such patients seems definitely indicated. The mechanism of action is not clear, but may reside in the ability of the drug to decrease gut tonus and thus attenuate the effect of a distending force.[10]

5. *Colonic disease:* One of the most common functional ailments to confront the gastroenterologist and the general physician is encompassed under the title "irritable colon syndrome." Its clinical manifestations include varying degrees of abdominal pain, diarrhea, constipation, "gassiness," bloating, excretion of mucus in the stools, etc. A great deal of human experimental work has aided greatly in ascribing much of this symptomatology to disordered motor patterns of the colon, varying in their type and degree at various times.[11] Thus diarrhea has been found associated with reduced motor activity of the left colon, permitting the unopposed contractions of the right colon to propel material through. Constipation, on the other hand, has correlated with increase in the "brake" action contractions of the sigmoid.[12] Pain is probably due either to distention of the gut or to areas of "spasm," or to both.

Anticholinergic drugs are often of great value in relieving this disordered

motility and constitute one of the mainstays in therapy of this syndrome. Empirically (and with some physiologic basis), it has been observed that such drugs are most effective in counteracting diarrhea and pain, and much less so in treating constipation.[13] Needless to say, use of these agents constitutes but one step in the ladder to successful management of such patients, and attention to diet, psychotherapy, sedation and the skilled intervention of the sympathetic physician must not be deëmphasized.

There is reason to believe that the physiologic mechanism described above for the production of diarrhea may also apply, at least in part, to dysenteries of other origin, such as chronic ulcerative colitis, amebiasis, bacillary enteritis, acute gastroenteritis, etc. Exhibition of anticholinergic drugs is often of great value in such conditions in ameliorating symptoms while other more specific therapy is being undertaken.

Experimental work indicates that anticholinergic drugs are also effective in inhibiting small bowel motor activity,[14] as well as that of the colon, and their use in functional motor derangements such as "small bowel diarrhea," and organic diseases such as regional enteritis, is frequently of benefit symptomatically.

B. *Cautions, Limitations and Relative Contraindications.*

1. *Urinary retention:* Not only do adequate doses of potent anticholinergic drugs depress intestinal muscle activity, but they also inhibit the action of the smooth muscle of the urinary bladder. In some patients this leads to difficulty in urination and inability to empty the bladder completely. In a few, especially those with partial urethral obstruction, as from prostatic hypertrophy, stricture, etc., acute urinary retention may be precipitated.[15] Caution must therefore be exercised in such subjects, and significant dysuria may contraindicate further use of drug therapy. In acute situations, such as pancreatitis, it may be desirable to have a retention catheter kept in place during the period of treatment with anticholinergic agents.

2. *Glaucoma:* Paralysis of the sphincter muscle of the iris is a common manifestation of the parasympatholytic activity of anticholinergic drugs, and the resulting mydriasis may, in the eye with already increased intra-ocular pressure, produce acute glaucoma. Attention to this possibility is therefore required on the part of the physician who uses such drugs, and they should be employed with extreme caution or not at all in cases suspected of having chronic glaucoma. Prior to therapy it is well to question every patient, especially the elderly, as to visual disturbances, lacrimation, ocular pain, etc., and to rule out chronic glaucoma by appropriate measures in those with suggestive symptoms.

3. *Coronary artery disease:* Mild to moderate tachycardia is not infrequently seen after oral administration of anticholinergic agents, and severe tachycardia sometimes follows their parenteral use. This results from block of the vagal influence on the heart and, in combination with coronary artery disease, may precipitate episodes of myocardial ischemia. Thus

angina pectoris has been reported aggravated by orally used anticholinergic drugs,[16] and the author has seen the precipitation of chest pain with transient electrocardiographic evidence of myocardial ischemia following the induction of tachycardia with intravenous administration. Caution is therefore indicated in the employment of such medications in the presence of impaired coronary blood flow, especially with parenteral administration, and in the presence of actual or potential shock, such as may occur with bleeding peptic ulcer or with acute pancreatitis.

4. *Drug idiosyncrasy and allergy:* Reports of toxic effects of the naturally occurring and synthetic anticholinergic drugs are remarkably few, when one considers their widespread use. Yet adverse effects do sometimes occur, and toxic psychoses and drug rashes have been reported for belladonna and atropine.[17, 18] Of the synthetic agents, apparently to date only methantheline has been incriminated in this regard, probably because it has been employed longer than most of the other potent synthetics and has had wider use. Drug rash and toxic psychosis (consisting chiefly of elation, visual hallucinations and disorientation) have been reported.[16, 19, 20] Of interest is a report in a patient of a curare-like reaction to oral methantheline, consisting of confusion, asthenia, coma, muscular flaccidity and areflexia.[21] This block of the nicotinic effect of acetylcholine has been observed in animals with both methantheline and propantheline bromide, and demonstrates the genuine anticholinergic action of such drugs. Obviously, idiosyncrasy to the anticholinergics constitutes a serious contraindication to their use.

5. *Bleeding peptic ulcer:* A most important compensatory mechanism in gastrointestinal hemorrhage consists of peripheral and splanchnic vasoconstriction to maintain blood pressure and circulatory competency. Anticholinergic drugs which interfere with ganglionic transmission would thus appear to be contraindicated during the acute stages of bleeding because of adverse effects they may have on compensatory sympathetic activity, with possible potentiation of shock. Reasonably large doses of parenterally administered atropine (long believed to have little or no ganglionic blocking action) have been demonstrated to produce postural hypotension and pooling of blood in the splanchnic and peripheral vascular beds of normal young subjects.[22, 23] At least part of this effect has been attributed to partial autonomic ganglionic block.[23] It would therefore appear wiser in the management of patients with severe bleeding ulcer to rely on gastric acid neutralization by food and antacids than to attempt acid suppression with anticholinergic drugs during the acute stages of bleeding. When circulatory competency is assured following cessation of hemorrhage, drug therapy may be worth while.

6. *Pyloric obstruction:* Gastric evacuation has been shown to depend on the development of pressure gradients between the stomach and duodenum as a result of muscular activity of the gastric wall.[24] Inhibition of such activity by anticholinergic drugs interferes with gastric emptying and, in the patient with pyloric obstruction due to ulcer, may increase the obstructive

symptoms.[25] If obstruction is not complete, acid inhibition with such drugs may promote ulcer healing and thus serve a beneficial rôle without aggravating obstructive symptoms. If a trial of drug therapy is used, careful attention should be given to signs of increasing gastric retention and anticholinergics should be discontinued if these signs develop. If this is not done, the stage of "decompensated" pyloric obstruction may be hastened, with attendant gastric atony and dilatation, vomiting, fluid and electrolyte imbalance, etc.

7. *Pyloric canal ulcer:* Peptic ulcer occurring in the pyloric canal frequently produces vomiting, presumably either as an "irritative" phenomenon or by actual pyloric obstruction through fibrosis or spasm. Roentgen and other evidence of gastric retention is common. As there is no evidence that anticholinergic drugs inhibit the spasm associated with inflammation, and as gastric evacuation depends more on gastric peristalsis than upon pyloric sphincter relaxation (as pointed out above), use of such drugs in therapy would appear, on theoretic grounds, to be at times contraindicated. Clinical experience bears this out and, in some cases, intractable vomiting and pyloric obstruction follow their use.[26] It behooves the physician to employ such agents cautiously, if at all, in this ulcer syndrome, and to recognize that therapy itself may be contributing to an unsatisfactory clinical response.

8. *Cardiospasm:* Physiologic mechanisms involved in the genesis of cardiospasm have received much attention in recent years, and considerable clarification of the nature of the disturbance has been made. These, plus anatomic studies, would indicate (a) that there is no evidence of "spasm" or muscle hypertrophy at the cardiac end of the esophagus in most such cases;[27] (b) that the entity involves a generalized disorder of esophageal motility with inadequate propulsion along the organ;[28] and (c) that the disease can be reproduced in animals by means of cervical vagotomy.[29] On theoretic grounds, then, anticholinergic drugs would appear of no value in the treatment of cardiospasm, and clinical experience confirms this in most cases. By inhibition of the already inadequate propulsive movements of the upper esophagus, such drug therapy would seem at times actually to be responsible for intensifying esophageal retention and symptoms of dysphagia.[30, 31]

Several other "motor" mechanisms for production of dysphagia have recently been elucidated by these studies, including "contractile ring of the lower esophagus"[32] and "dysrhythmia of the esophagus."[31] In neither of these situations has anticholinergic drug therapy been of benefit, and symptomatology has in some instances been increased by its use.

Conclusions

No attempt is made in this review to cover exhaustively the proper and improper employment of anticholinergic drugs in the management of gastro-

intestinal disease. Rather, the purpose is to illustrate with appropriate examples the niche into which such therapy does or does not fit. So prevalent and at times ritualistic is the employment of anticholinergic drugs that the unwary physician may come to rely too heavily on them and tend to overlook those situations where their use can be expected to accomplish nothing or to be actually contraindicated. While they may be of tremendous therapeutic efficacy when exhibited under the proper indications, illogical use may result in therapeutic failure or even harm. As with any pharmacologic agent, rational employment of anticholinergic drugs in the management of gastrointestinal disease requires careful consideration of the underlying pathophysiology of the disease, knowledge of the actions and toxicity of the drug, and the ability to direct the bow where the arrow is needed.

SUMMARIO IN INTERLINGUA

Drogas anticholinergic es extensemente usate in le tractamento de un numero de differente morbos gastrointestinal. A vices lor uso deveni un ritual sin le base de un appropriate consideration del subjacente pathophysiologia del morbo e del potentialmente adverse effectos de iste drogas. Le objectivo del presente articulo es passar brevemente in revista alicunes del indicationes e contraindicationes e limitationes del therapia a drogas anticholinergic.

Le potentia de tal drogas de deprimer le production de acido gastric e de inhibir le activitate motori del intestino provide desirabile effectos therapeutic in conditiones como ulcere peptic, pancreatitis, e un numero del disturbationes functional del intestinos. Le syndrome del discarga jejunal e diarrhea beneficia frequentemente del administration del drogas, al minus symptomaticamente.

Adverse effectos lateral—retention urinari, mydriasis, e tachycardia, etc.—limita le utilitate del drogas anticholinergic in certe casos. Alicun occurrentias de allergia e idiosyncrasia in le reaction a iste drogas ha essite reportate. In casos de ulcere sanguinante le effecto del drogas pote esser un obstruction de mechanismos compensatori in consequentia de blocage ganglionic e inhibition sympathic. Intensification de obstruction pyloric pote resultar del administration de drogas anticholinergic que etiam aggrava a vices le symptomas de dysphagia in casos de cardiospasmo e altere disturbationes esophageo-motori.

Le uso correcte de drogas anticholinergic in le therapia de morbo gastrointestinal require le comprension del subjacente disturbationes physiologic. Illo presuppone le cognoscentia e le consideration del establite effectos e del documentate toxicitate de ille drogas.

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POSTURAL ADJUSTMENTS AND PROTEIN EXCRETION BY THE KIDNEY IN RENAL DISEASE *

By S. Edward King, M.S., M.D., F.A.C.P., *New York, N. Y.*

Introduction

Protein excreted by the kidney is derived from the serum proteins filtered through the glomerulus.[1] Considerable evidence [2, 3] suggests that protein may be re-absorbed from the glomerular filtrate by the renal tubules. Divergence of opinion exists as to whether this tubular re-absorptive function is active normally, and as to its relative importance in renal disease. Protein may be excreted by the normal kidney during congestive heart failure [1] following exposure to cold,[4] after exercise,[5] and under various conditions producing considerable alterations in the renal circulation, including ischemia from the effect of adrenal medullary amines.[6]

Over the long term, protein excretion in chronic renal disease closely reflects changes in the underlying renal pathology.[7] In the healing stage of nephritis, proteinuria first diminishes or disappears from the recumbent night specimens.[8, 9] Increased proteinuria usually indicates progressing renal disease. The intense proteinuria of the nephrosis syndrome has been variously ascribed by some to tubular injury,[2, 10] by others to increasing glomerular permeability.[11–13] Other determinants of protein excretion by the kidney include alterations in the chemical and physical structure, and concentration of the individual fractions of the serum proteins which may compete with each other for tubular re-absorption.[14] Hypothetic concepts of glomerular pores, which under certain conditions would permit escape of protein macromolecules, have been strengthened by the observations of Wallenius [15] and others.[8]

It is sometimes stated that protein excretion tends to diminish in advanced renal disease.[16, 17] Ordinarily, this effect is apparent rather than real, being due to dilution of excreted protein by polyuria attending renal insufficiency. Bing [18] emphasized the necessity for gauging urinary protein excretion by the rate of excretion (quantity over given time) rather than by the varying concentration so dependent upon variations in urine flow.

Further observations [19, 20] have confirmed the opinion that persisting proteinuria—continuous day and night—generally accompanies overt and significant but not necessarily advanced organic renal disease. However, the distinction between continuous and fixed "orthostatic" proteinuria may

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Requests for reprints should be addressed to S. Edward King, M.D., 30 East Fortieth Street, New York 16, N. Y.

be one more of degree than of kind, since various organic renal disorders may be characterized by inconstant "orthostatic" patterns of protein excretion.[9, 19] The "orthostatic" type of proteinuria may be found with latent, subsiding glomerulonephritis, and early pyelonephritis, and in congenital and early vascular and collagen disease of the kidney.[19] In view of the varying underlying renal pathology, prognosis based solely upon this abnormal finding is scarcely justified. Frequently, under ordinary clinical conditions, proteinuria due to manifest renal disease may erroneously be considered orthostatic. Chronic (persistent) proteinuria of any pattern may be the only clinical evidence of renal disease over long periods, and should not be dismissed lightly without adequate study.

There have been relatively few studies on the effect of posture upon protein excretion in established renal disease.[18, 13, 19] Bing [18] emphasized the postural changes in urine protein concentration and excretion with increased proteinuria during the day. His data also suggest some relationship between protein excretion and the rate of glomerular filtration at low filtration levels.

Lathem, Roof, Nickel and Bradley [13] reported diminished protein excretion on standing in their subjects with advanced renal disease. Absence of any uniform postural pattern of protein excretion in chronic renal disease was previously noted and was ascribed to variations in renal functions.[19] Relationship was suggested between increased glomerular pressure, as indicated by the elevated filtration fraction, and the augmented proteinuria of standing.[9, 19]

The significance of proteinuria in Bright's disease has been considered limited, usually to its utility as an index of the severity and trend of the renal disease. Evidence previously reviewed,[19] as well as analogy with the obstructive tubular nephropathy of myeloma and the hemoglobinuric kidney, suggests that continued excretion of protein may, in itself, at times contribute to chronicity and acceleration of renal disease.

The effect of quiet standing upon the renal excretion of protein was studied in 27 subjects with relatively moderate or mild renal disease. Urinary protein excretion was found to be increased on standing in subjects with initially modest recumbent proteinuria and normal renal function. Excretion of protein was either unaltered or slightly diminished in patients with more intense proteinuria or impaired renal function. These posturally induced changes in the rate of protein excretion have been related to corresponding alterations in renal functions and dynamics.

Methods and Materials

The subjects were young males, usually referred for study because of proteinuria or known renal disease. Four were hospital patients with nephritis. None was bedfast. All ambulatory patients were apparently

in excellent health. The diagnosis of orthostatic proteinuria had been previously entertained in some because of the more conspicuous morning proteinuria. Subjects with minimal night and recumbent proteinuria (below 10 mg.%) were not included in this report.

The following clinical conditions were included: chronic constant proteinuria of undetermined origin (urologic disease excluded), nine cases; chronic glomerulonephritis with mild proteinuria, nine cases; subsiding acute glomerulonephritis, two cases; chronic pyelonephritis, three cases; chronic nephritis with marked proteinuria, many casts but few red cells without edema, three cases; and nephrosis syndrome, one case.

All subjects had one or more serial urine protein pattern tests,[19] with supervised multiple urines tested for albumin, several fresh microscopic examinations, and Addis quantitative sediment determination. Clinical tests of renal function usually included blood urea nitrogen (or creatinine clearance), intravenous phenolsulfonphthalein, maximal urinary specific gravity and, frequently, intravenous urography. Clinical tests were omitted in instances when more precise evaluation of renal function by clearance of inulin and para-aminohippurate (PAH) were performed.

Clearance of inulin and PAH and protein excretion rates was determined in 14 subjects in the basal hydropenic state (table 1). A low and relatively constant urine flow was assured by moderate restriction of fluid, salt and protein for 12 hours. Clearances were determined during two or three 20-minute control periods in the supine position, and for one or more similar periods in erect lordosis, erect kyphosis or tilt. Orthostasis was discontinued in three subjects who complained of severe discomfort, sweating or faintness in all instances after lordosis. Excluding these three, there were 15 additional clearance observations, 10 in erect lordosis or tilt, and five in erect kyphosis.

Urine specimens were collected by catheterization, traumatic hematuria as a possible source of protein being excluded by microscopic examination and rapid chemical examination for blood (tablets of orthotoluidine). Quantitative protein was determined by the biuret method of Foster, Rick and Wolfson [21] on urines qualitatively positive with sulfosalicylic acid reagent. Results were checked periodically by micro-Kjeldahl. Specimens with transmission under 98 (10 mg.%) in undiluted urines were considered negative. Inulin was determined by a modification of Harrison's method, described by Goldring and Chasis,[22] and para-aminohippurate by the method of Smith, Finkelstein, Aliminosa, Crawford and Graber.[23]

Thirteen ambulatory subjects with chronic renal disease were studied solely for the effect of quiet standing upon protein excretion (table 2). While in the basal hydropenic state the bladder was emptied during recumbency, the procedure being discontinued in the occasional instance when complete bladder emptying was not assured. Timed, voided, supine and orthostatic urine specimens were collected with the patient under continuous

TABLE 1

Alterations in Renal Functions and Proteinuria on Standing in Renal Disease

Case Number	S.A.M.	Clinical Diagnosis	Procedure	Renal Functions				Proteinuria	
				C_{inulin} ml./min.	C_{pah} ml./min.	FF	V ml./min.	mg./%	P mg./min.
1	1.99	Acute nephritis (RBC, casts, BUN, 22 mg.)	Control[1]	79	433	0.18	3.01	41	1.20
			Standing[2] (L) 20/27	57	279	0.20	0.89	194	1.74
2	1.71	Chronic nephritis (RBC)	Control	133	515	0.26	0.66	31	0.21
			Standing (K) 20/24	138	369	0.37	0.54	44	0.24
3	1.58	Constant proteinuria (normal sediment)	Control	100	611	0.16	0.86	20.2	0.17
			Standing (L) 15/21	73	437	0.17	0.58	110.2	0.64
4	1.69	Constant proteinuria (normal sediment)	Control	140	717	0.20	1.11	19	0.18
			Standing (L)* 6/18	138	494	0.29	0.72	28	0.20
			Control	109	654	0.17	0.68	24	0.16
			Standing (K) 15/19	104	526	0.20	0.74	38	0.28
5	1.92	Constant proteinuria (normal sediment)	Control	78	465	0.18	0.48	42	0.21
			Standing (L)* 4/26		460		0.57	50	0.28
6	1.94	Constant proteinuria (normal sediment)	Control	112	631	0.17	0.98	23	0.27
			Standing (L) 15/19	73	333	0.22	0.38	113	0.43
			Control	120	601	0.20	0.52	84	0.38
			Standing (K) 15/23	95	374	0.25	0.30	158	0.47
7	1.74	Chronic nephritis (WBC and RBC)	Control	110	445	0.24	1.13	13	0.15
			Standing (L) 13/25	83.3	288	0.29	0.84	90	0.76

[1] All control clearance values are averages of two or more determinations in quiet supine recumbency.

[2] Standing clearance periods in kyphosis (K), lordosis (L) and tilt were terminated on return to recumbency. Duration of standing (minutes) indicated as fraction of total period.

* Fainted.

† Perspiring and weak.

TABLE 1 (*Continued*)

Case Number	S.A.M.	Clinical Diagnosis	Procedure	Renal Functions				Proteinuria	
				C_{inulin} ml./min.	C_{pah} ml./min.	FF	V ml./min.	mg./%	P mg./min.
8	1.60	Chronic nephritis (many RBC, casts and epith. cells)	Control	90	492	0.18	0.50	30	0.15
			Standing (L) 27/46	66	349	0.20	0.35	100	0.35
			Standing (K) 10/19	72	344	0.21	0.42	147	0.62
9	1.84	Constant proteinuria (normal sediment)	Control	110	459	0.24	1.20	12	0.14
			Standing (L) 15/21	78	354	0.28	1.24	27	0.33
10	1.66	Constant proteinuria (normal sediment)			Tm PAH				
			Control	80	74		2.13	13	0.28
			Standing (L) 15/16	78	69		1.77	25	0.44
			Recovery	82	72		2.00	14	0.29
11	1.61	Acute nephritis subsiding (RBC and casts)	Control	95	680	0.14	0.59	65	0.38
			Standing (K)† 15/22	67	480	0.14	0.68	44	0.30
			Standing (L)† 23/29	58	364	0.16	0.38	182	0.72
12	1.60	Chronic nephritis (casts and RBC)	Control	124	825	0.15	2.44	57	1.40
			Standing (L)* 9/17	110	783	0.14	1.82	42	0.76
13	1.81	Chronic nephritis (RBC)	Control	119	648	0.19	0.66	30	0.30
			Tilt-26/29†	99	474	0.21	0.59	45	0.27
14	1.62	Chronic nephritis, nephrotic syndrome—occasional RBC, many casts—BUN 32 mg.	Control	28	254	0.11	1.19	458	5.42
			Standing (L) 13/19	21	189	0.11	0.72	561	4.04

TABLE 2—The Effect of Posture upon Protein Excretion in Renal Disease

Case Number	Diagnosis and Clinical Features	Recumbent-Control				Standing			
		Duration minutes	V ml./min.	Protein mg./%	Protein mg./min.	Duration minutes	V ml./min.	Protein mg./%	Protein mg./min.
15	Chronic nephritis (RBC and casts)	91	1.10	28	0.25	73	0.52	93	0.48
16	Chronic pyelonephritis[1] (white and epith. cells)	84	1.00	23	0.23	53	0.68	53	0.36
17	Chronic nephritis (many RBC and casts)	92	0.81	19	0.15	58	0.55	33	0.18
18	Chronic pyelonephritis[1] (many WBC and casts)	95	1.40	58	0.81	39	0.90	150	1.40
19	Chronic nephritis—few RBC and casts —hypertension	81 80	0.43 1.50	Trace 20	— 0.30	46 90	0.87 0.24	80 247	0.70 0.61
20	Constant proteinuria, sp. gravity 1.016	53 79	0.79 1.60	23 22	0.18 0.35	54 45	0.30 0.84	54 46	0.16 0.39
21	Chronic nephritis (RBC and casts)	90	1.00	22	0.22	30	0.97	47	0.46
22	Chronic pyelonephritis[1] (WBC and casts)	100 73	0.79 1.10	47 35	0.36 0.39	47 19	0.60 1.10	70 44	0.42 0.48
23	Constant proteinuria (few RBC and casts)	82 —	0.39 —	42 —	0.16 —	60 43	0.23 1.10	377 51	0.87 0.56
24	Constant proteinuria[1] (normal sediment)	64 82	0.75 0.85	57 55	0.43 0.48	48 65	0.69 0.42	112 320	0.77 1.22
25	Chronic nephritis (many RBC—frequent casts) BUN, 21	69 —	0.70 —	237 —	1.65 —	68 41	0.32 0.49	640 560	1.94 2.74
26	Chronic nephritis (many casts and epith. cells) BUN, 18.0	62	1.40	258	3.58	24	0.75	730	5.50
27	Chronic nephritis—many casts—occasional RBC, Sp. gravity 1.016–18	60 87	0.38 0.53	550 340	2.10 1.70	79 86	0.41 0.24	620 740	2.50 1.80

[1] = Normal urograms. Renal function and blood pressure, normal unless otherwise indicated.

supervision. In over half of this group the procedure was repeated on the subsequent day. The rates of protein and sediment excretion were determined under these conditions without possibility of hematuria or mucus from catheter irritation. Urine specimens of low specific gravity (under 1.018) and those not presenting diminished volume rate (antidiuresis) on

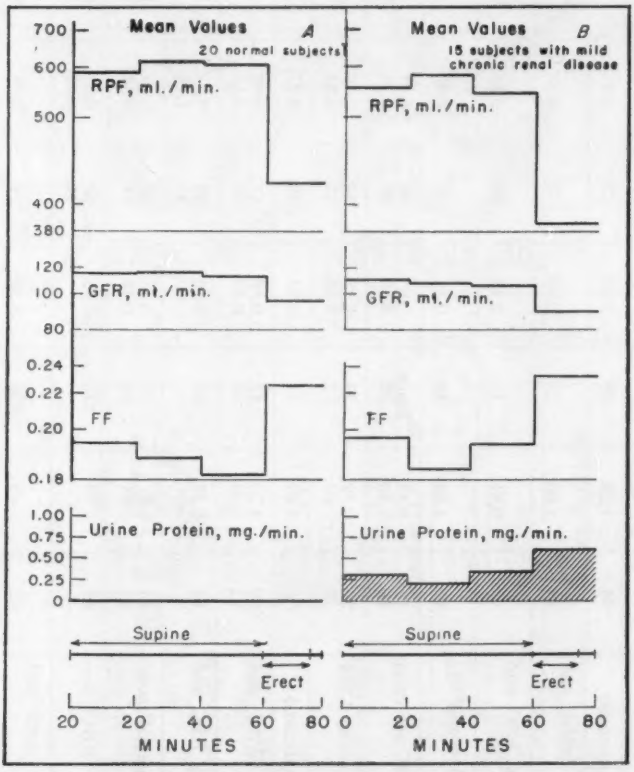


FIG. 1. A. Mean values of renal plasma flow, glomerular filtration rate and filtration fractions in 20 normal subjects, while supine and on standing, are presented. Postural alterations were statistically significant. B. Corresponding values in 15 patients with chronic renal disease and normal function are presented. The similarity in postural renal adjustments, occurring in normal subjects and in patients with mild chronic renal disease, is evident. The mean rate of protein excretion in B increased moderately but significantly during orthostasis. A direct relationship is postulated between alterations in protein excretion and these hemodynamic adjustments.

standing were excluded. The procedure was discontinued in several subjects developing postural hypotension and syncope. Urine proteins were examined by methods previously described, and Addis counts were performed in duplicate on aliquots of freshly voided recumbent and orthostatic specimens.

It is improbable, under these conditions, that subjects with orthostatic proteinuria, as ordinarily defined, were included among the chronic unspecified continuous proteinurias. The subjects in this study represented chronic renal disease in an early, functionally well compensated stage, without anemia, electrolytic imbalance or cardiovascular complications. Observations upon such ambulatory subjects in good general health are at least as valid as are those on subjects in a more advanced stage of renal disease.

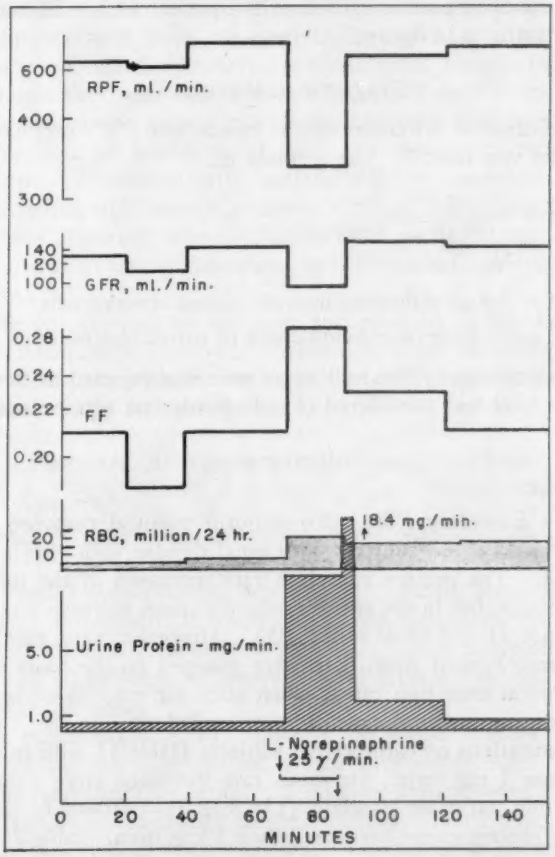


FIG. 2. Increase in the filtration fraction (from 0.21 to 0.28) in recumbency, induced by intravenous norepinephrine in a patient with mild chronic glomerulonephritis, augmented protein excretion from 0.5 mg./min. to approximately 9.5 mg./min. during the period of infusion. Protein excretion continued to increase, reaching 18.0 mg./min. in a specimen collected 5 minutes later. Proteinuria, at a rate of 2 mg./min., persisted for approximately 30 minutes after norepinephrine was discontinued. Initially mild hematuria was slightly increased, returning to previous levels the following day. The hematuria did not contribute to the proteinuria.

Many irrelevant and systemic complications of advanced renal disease are excluded under these circumstances.

Mean values of inulin and PAH clearance observations on 20 normal subjects during recumbency and orthostasis, to be reported,[25] were used in constructing part A of figure 1. Part B is based upon the mean values for observations in table 1, with mild proteinuria (under 1 mg./min.), normal renal function, and not exhibiting orthostatic hypotension or syncope.

The effect of presumably increasing glomerular pressure by intravenous l-norepinephrine upon protein excretion in a patient with mild latent chronic nephritis is illustrated in figure 2.

Statistical Method

The significance of difference of the means test ("t" test) between correlated samples was used.[24] The formula is:

$$t = \frac{\Sigma D}{\sqrt{\frac{N\Sigma D^2 - (\Sigma D)^2}{N - 1}}}$$

D = Actual difference between paired observations

N = Number of individual sets of paired observations

Level of significance: The null hypothesis was rejected at the 1% level. The 2 to 5% level was considered of only borderline significance.

Results

Proteinuria:

1. *Protein Excretion Rate.* No uniform postural response was noted in 35 observations in 27 subjects with renal disease with varying intensity of proteinuria. The protein excretion rate increased in the majority following orthostasis, but in the entire group the mean increase was of borderline significance ($t = 2.33$ $P = .02$–$.05$). However, very significant correlations became evident when data were grouped on the basis of intensity of control protein excretion rates; when also, for reasons to be discussed, subjects developing postural syncope were excluded.

In 11 observations on catheterized subjects (table 1) with initial protein excretion below 1 mg./min., the mean rate increased from 0.26 mg./min. to 0.48 mg./min. on quiet standing ($t = 3.12$ $P = .01$–$.02$). In 15 other subjects with protein excretion rates below 1 mg./min. (table 2), the mean protein excretion rate under these conditions increased from 0.38 mg./min. to 0.62 mg./min. ($t = 3.71$ $P < .01$). In seven observations on subjects with initial proteinuria exceeding 1 mg./min. (tables 1 and 2), protein excretion rates on standing increased in four, were unaltered in one and decreased in two. The mean change was insignificant—from 2.49 mg./min. to 2.61 mg./min.

Protein excretion rates were studied in 12 subjects during consecutive

periods of recumbency and revealed no significant alterations (table 1) ($t = 0.11$ $P > .10$). Similar insignificant differences were obtained in 11 subjects during rest periods at 24-hour intervals ($t = 1.05$ $P > .10$).

2. *Concentration of Urine Protein.* If we exclude subjects with postural syncope, in catheterized subjects (table 1) with initially mild proteinuria the mean urinary protein concentration increased significantly—from 39 mg.% to 112 mg.% during orthostasis ($t = 4.65$ $P < .001$). A similar increase in protein concentration occurred in observations in table 2: from 36 mg.% to 121 mg.% ($t = 3.19$ $P < .01$). Average concentrations of urine protein increased three- or fourfold, but in some instances a much greater increase occurred. In seven subjects with initially intense recumbent proteinuria the mean concentration increased only from 256 to 424 mg.% as the mean urine volume rate diminished from 1.37 to 0.74 ml./min.

In summary, under similar basal conditions, protein excretion remained quite constant. In subjects with initially mild or moderate proteinuria, excretion increased significantly on quiet standing. No conspicuous effect of posture was observed when initial proteinuria was intense. Protein concentration was primarily influenced in a reciprocal manner, by the rate of urine flow.

No consistent changes in sediment excretion by Addis counts or individual specimens were observed in transition from recumbency to standing. In four subjects with intense proteinuria, hyaline and granular casts increased considerably on standing.

Postural Alterations in Renal Function

A. *Postural Syncope.*

Occasionally, distressing subjective symptoms—including weakness, sweating, vertigo and sudden syncope occur during quiet standing. Postural (orthostatic) syncope with hypotension [19] (acute postural circulatory insufficiency [18]) is frequent in individuals with vasomotor instability and in acutely or chronically ill bedfast patients. These symptoms were observed in 11 of 20 subjects with severe renal disease reported by Lathem, Roof, Nickel and Bradley.[18]

In three patients (table 1), faintness or actual syncope necessitated termination of the standing period, which thus represented but a small fraction of the total clearance period. Mild symptoms appeared in two other instances. No consistent change in renal plasma flow or glomerular filtration rate was observed in these patients. Variations in protein excretion in these instances were insignificant. For reasons to be discussed, systemic and renal readjustments of this nature have not been considered representative and have been excluded from the statistical data.

B. *Alterations in Renal Functions during Quiet Standing (table 1).*

1. *Glomerular Filtration Rate (GFR).* A moderate reduction in the glomerular filtration rate (as measured by clearance of inulin) occurred

on standing, with a mean diminution of 25.5%. The difference of the means from the control of 105 ml./min. to 79 ml./min. was highly significant statistically ($t = 5.36$ $P < .001$).

2. *Renal Plasma Flow* (RPF). A somewhat greater reduction in renal plasma flow (measured by clearance of PAH) occurred on standing, with a mean diminution of 30.8%. The difference of the means from the control, of 557 ml./min. to 386 ml./min., was highly significant statistically ($t = 7.28$ $P < .001$).

3. *Filtration Fraction.* Alterations in this derived ratio (GFR/RPF), although percentage-wise less conspicuous, were consistent and significant. There was an increase of 20.0% from the mean of all values during recumbency to the mean on orthostasis. Comparison between the mean during the final recumbent period (usually nearest basal level) and that on standing accentuated the percentage increase slightly (23.5%). The increase in filtration fraction on standing in these observations was statistically significant ($P = 0.01$–0.02), as was it in normals and in subjects with orthostatic proteinuria.[25] This was not observed in patients with impaired renal function.

Proteinuria and Renal Functions

No clear or consistent relationship was noted between alterations in discrete renal functions and protein excretion on changing from recumbency to quiet standing. Augmented protein excretion rates occurred in four subjects with considerable reductions in RPF (55, 45, 50 and 35%). Protein excretion diminished in three subjects with considerable reduction in glomerular filtration rate (45, 57 and 35%). In four subjects with initially impaired glomerular function, evidenced by recumbent glomerular filtration rates below 60 ml./min., protein excretion was either unaffected or diminished by posture.

Note: Actual reductions in renal functions during orthostasis were probably greater than are recorded in this study for the following reasons. A small portion of urine collected during standing probably was secreted while supine, i.e., in "dead space." In part, anhydremic conditions and relatively constant low rates of urine flow may have reduced the magnitude of this error. To have discarded an arbitrary volume or an amount secreted after an appreciable period of standing would have excluded the period believed to represent the maximal effects of standing.

A second source of error arose in the occasional necessity for terminating collection of the orthostatic urine specimens in recumbency, particularly when the patient felt faint or uncomfortable. The ratio of the time that the patient stood to this entire clearance period has been indicated as a fraction in the procedure column in table 1. Periods with low ratios of time in orthostasis to the total clearance period usually showed minimal increase in the filtration fraction above recumbent levels.

Discussion

Urinary excretion of protein has been shown to be significantly increased on quiet standing in patients with renal disease and normal function. Postural effects are less conspicuous in patients with more intense protein-

uria (over 1 mg./min.) and/or impaired renal function. Lathem and associates [18] reported protein excretion to be diminished on standing in chronic renal disease. Their observations, however, were largely limited to bedfast patients with advanced disease, often with extremely low rates of glomerular filtration. Also, over half of their patients developed postural hypotension and syncope, conditions which are not accompanied by customary or representative renal adjustments to postural change. Increased protein excretion was not observed in those patients in this study developing this atypical postural hemodynamic response.

Variations in concentration of urinary protein are largely dependent upon alterations in urinary volume. Protein concentrations were greatly increased on standing during the usual orthostatic antidiuresis. In some instances, a tenfold increase in urine protein concentrations followed standing. This increase—often out of proportion to the actual increment of protein excretion—may be responsible for fallacious concepts concerning "postural proteinuria." Similar results were obtained by Lathem and associates, who observed increased protein concentrations in the urine of severe nephritics on standing when protein excretion rates actually had diminished. Clearly the protein excretion rate is the only reliable estimate of protein loss in the urine.

Ordinarily, renal adjustments to quiet standing involve significant diminution in renal blood flow and, to a less degree, in the glomerular filtration rate. The general response is identical in normal subjects, in patients with orthostatic proteinuria and in those with overt renal disease without insufficiency.[25, 26] Diminished renal blood flow on standing represents the renal component of systemic vasoconstriction,[1] probably mediated through the sympathetic nervous system. The renal hemodynamic response to intravenous epinephrine is similar to that during orthostasis.[1, 6]

Although both effective renal plasma flow and glomerular filtration are diminished, reduction is not equal in degree or simultaneous. Renal plasma flow declines sharply and abruptly; glomerular filtration diminishes gradually. The inulin/PAH clearance ratio or filtration fraction (FF) is accordingly increased during early orthostasis. Maximal levels for this ratio may escape observation when standing clearance periods are prolonged and fatigue develops. Ordinarily, glomerular filtration is relatively well maintained on standing, despite considerable diminution in renal plasma flow.

Usually the filtration fraction is not subject to great variations.[1, 22] Indeed, wide oscillations would scarcely be anticipated if this ratio reflects glomerular pressures, as is generally assumed in the relatively normal kidney. However, an increase of over 50% in the filtration fraction with renal ischemia follows large doses of intravenous epinephrine and norepinephrine.[1, 6] An increased filtration fraction has been reported early in hypertension,[22] and in hypertensive patients during the elevated arterial blood pressure with "traumatic" psychiatric interview.[27]

Renal functional adjustments with orthostatic hypotension and syncope differ basically from those during quiet standing.[1, 19, 25] Technical factors also modify observed values. When fainting (cerebral anoxia) occurs early during orthostasis, inclusion of urine voided in the recovery time with the total clearance period dilutes and negates the usual orthostatic pattern. When symptoms of cerebral anoxia follow prolonged standing or tilt, glomerular filtration and renal plasma flow are both markedly and proportionately diminished, suggesting afferent renal vasoconstriction.[1, 8, 25] Renal alterations with syncope cannot be accepted as representative of the usual adjustments to quiet standing.

With severe glomerular disease the filtration fraction is reduced because of diminished glomerular filtration rate from organic obliteration of the glomerular bed.[7, 22] With extensive tubular damage, extraction of para-aminohippurate is impaired and the clearance of this substance fails to measure renal plasma flow. Inordinately high filtration fractions under such conditions are without meaning. In general, with advanced renal disease the filtration fraction probably ceases to reflect changes in glomerular pressure.

Alterations in renal plasma flow, glomerular filtration and perhaps other functions presumably control postural changes in protein excretion in renal disease. The relative importance of the many factors affecting protein excretion by the kidney can only be surmised. It appears improbable that the observed diminution in renal blood flow on standing is sufficient to influence glomerular permeability (or tubular reabsorptive function) through anoxia. Orthostatic changes in tubular functions, as measured by Tm PAH and Tm glucose, have not been observed by us in normal or proteinuric subjects.[25] Orthostatic depression of Tm glucose reported in renal disease [18] may represent the effects of postural hypotension and syncope.

Increased glomerular permeability is generally considered the major determinant of protein excretion in renal disease.[11–13, 15] Impressive evidence suggesting graded molecular sieving of protein, apparently through pores in the glomerular membrane, has been presented by Wallenius.[15] Using dextrans of graded molecular weight, he found an upper limit not capable of passing the normal glomerular membrane. In proteinuric subjects, however, larger dextran molecules appeared in the urine. These and other observations [12] suggest that proteinuria in renal disease usually results from increased permeability or porosity of the glomerular membrane. Admittedly,[12] they do not exclude some degree of tubular reabsorption of protein.

The chemical and physical structure of the serum proteins [10] and their concentrations probably condition their filtration through the glomerulus. The various protein fractions act independently and apparently competitively [14] in this process. The total available glomerular filtration surface becomes a limiting parameter only when greatly restricted in advanced renal

disease. At this stage protein excretion appears to become directly related to alterations in the glomerular filtration rate despite high porosity for protein.[13, 18]

The intraglomerular hydrostatic pressure is a filtration force, which also may influence the passage of protein through the glomerular membrane. Chinard [28] suggested that glomerular permeability for protein may be increased by rising glomerular pressure which, by stretching the membrane, would enlarge the intercellular interstices or pores. This mechanism would explain the proteinuria following the intravenous medullary amines in normal subjects and other conditions associated with a sharp increase in glomerular pressure. Irrespective of the precise mechanism, the hypothesis that protein filtration through the glomerulus is favored by increase in glomerular pressure is compatible with current observations.

Although proteinuria in renal disease is generally conceded to be due to increased glomerular permeability or porosity,[11, 12, 13, 15] other factors may become important, particularly over short periods. Under certain conditions it has been assumed here that moderate alterations in glomerular pressure, such as attend bodily change in posture, may significantly affect the filtration and excretion of protein by the kidney. These specific conditions are mild to moderate glomerular lesions with corresponding mild porosity and proteinuria.

With sufficiently extensive lesions, proteinuria may be continuous, although increased during orthostasis and activity. In patients with minimal renal lesions, proteinuria may be absent during recumbency, appearing regularly on arising and activity (orthostatic proteinuria). This concept is in accord with clinical observations on many patients with orthostatic proteinuria and frequent evidence of associated renal disease.

In accordance with this hypothesis, marked increase in glomerular pressure experimentally induced by infusion of the adrenal medullary amines (50%) would increase protein filtration in normal man, inducing transient proteinuria. This is the case.[6] Similar conditions may prevail physiologically under stress in normal persons or predisposed individuals, thus accounting for the common transient proteinuria. It has been shown that the quantity of the adrenal amines excreted in the urine under stress [29] may approximate that excreted in pheochromocytoma, a disorder in which proteinuria is frequently present.[6]

The effect of graded increase in filtration pressure produced by infusion of adrenal amines upon protein excretion in mild renal disease is under investigation. Proteinuria has been induced in patients with orthostatic proteinuria while recumbent, at rates exceeding those following orthostasis, a general parallelism being evident between protein excretion and alterations in the filtration fraction. Augmented protein excretion has been observed also in patients with continuous proteinuria in chronic renal disease by infusion of adrenal amines with increase in the filtration fraction. Observa-

tions in a patient with mild chronic nephritis are summarized in figure 2. Protein excretion increased from a rate of 0.5 mg./min. to a mean rate of 9.8 mg./min. during infusion of l-norepinephrine. As previously observed,[6] proteinuria persisted after the infusion was discontinued, in this instance for half an hour. Actually a peak rate of 18 mg./min. was observed in urine secreted for a short period after the infusion was discontinued.

Presumably through vasomotor control of the afferent and efferent glomerular arterioles, the sympathetic nervous system and adrenal medullary amines adjust the glomerular circulation and pressure to various stressful and more routine conditions, such as those during bodily postural change.

Parallelism between mean alterations in the filtration fraction and urinary protein excretion in 15 patients with chronic nephritis is shown in B, figure 1. Both alterations were statistically significant, and a causal relationship between them is suggested. Although often present, this relationship is not evident in every subject. Technical difficulties in demonstrating the relatively modest changes in the filtration fraction have been discussed. Unless tubular reabsorption of filtrate protein under these conditions is negligible, perfect linear correlation between increments in glomerular pressure (FF) and the rate of protein excretion would not be anticipated. Finally, a complex membrane equilibrium is involved which would normally not follow a simple linear relationship.

A generally uniform pattern of renal hemodynamic adjustment to standing is suggested by these and other data.[25, 26] Exceptions are renal insufficiency and orthostatic hypotension with syncope. The normal orthostatic pattern is characterized by relatively maintained filtration, despite an immediate considerable reduction in renal blood flow resulting in an elevated filtration fraction, which may express corresponding increase in glomerular pressure in the well functioning kidney. It will be noted that the mean alterations in renal plasma flow and glomerular filtration are almost identical in patients with mild chronic renal disease (B, figure 1) and 20 normal subjects (A, figure 1). Similar patterns have been found in approximately 40 patients with orthostatic proteinuria who did not develop postural syncope.[25] Mean alterations in all three groups were statistically significant.

It is believed that diurnal and postural alterations in protein excretion in patients with varying degrees of renal injury, short of renal insufficiency, may be related to these adjustments in renal functions and intraglomerular pressure.

Summary

The excretion of urinary protein and renal hemodynamic and functional adjustments to quiet standing (orthostasis) were studied in 27 young patients with relatively mild chronic renal disease. Excluding six hospital patients with recent nephritis, the majority were asymptomatic and characterized mainly by persistent, continuous proteinuria.

Excretion of protein was significantly increased on standing in patients with modest proteinuria (under 1 mg./min.) and good renal function. More intense proteinuria did not appear to be greatly influenced by postural change.

Alterations in urine protein concentrations depend primarily upon the rate of urine flow and in themselves are completely unreliable often leading to serious clinical error.

Protein excretion in renal disease probably is determined by various factors, of which the severity of the renal lesions and resulting glomerular permeability or porosity is dominant.

Other conditions being constant, alterations in glomerular pressure may be significant determinants of protein filtration and excretion by the kidney.

A direct and significant relationship between alterations in the filtration fraction (glomerular pressure) and in the rate of protein excretion by the kidney is suggested by these data. Considerations indicating why perfect correlation cannot be anticipated have been discussed.

A uniform pattern of orthostatic adjustment involving increase in the filtration fraction (glomerular pressure), is postulated in the well functioning kidney.

Postural alterations in urinary protein excretion in renal disease are believed related to this customary pattern of orthostatic hemodynamic adjustment.

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SUMMARIO IN INTERLINGUA

Esseva demonstrate que le excretion renal de proteina in patientes con grados moderate de proteinuria e bon functiones renal se augmenta significativemente in le position erecte in comparation con le valores pro le position jacente. Intense grados de proteinuria non pare esser alterate significativemente per alterationes del postura, sed patientes con insufficientia renal monstra a vices un diminution del excretion de proteina quando illes se trova in position erecte.

Variationes del excretion de proteina in morbo renal, in tanto que illos resulta de alterationes del postura, ha recipite pauc attention clinic. Isto se explica in alte grados per le usual costume clinic de mesurar proteinuria per mesurar le concentration del proteina excernite plus tosto que le proratas de ille excretion. Variationes del fluxo urinari que affice le concentration de proteina in senso inverse pote resultar in serie errores clinic. In patientes con nephritis chronic e leve grados de proteinuria on pote supponer le existentia de un "proteinuria orthostatic." Le relative basse grados de proteinuria in position jacente pote escappar completemente al observation o parer evalutabile como tracia insignificative, specialmente si specimens partial de character dilutionate es examinate. In le position erecte, le antidiurese costumari con basse valores del fluxo urinari e un genuin augmentation del excretion de proteina pote resultar in un considerabile magnification del concentration urinari de proteina.

Variationes in le proratas del excretion urinari de proteina reflecte alterationes del hemodynamica renal. Conditiones que induce un proteinuria transiente in sub-

jectos normal e que augmenta le excretion de proteina in patientes con morbo renal es characterisate per marcate grados de vasoconstriction renal con relativemente ben mantenite filtration glomerular. Le presentia de un augmentate pression intraglomerular es supponite sub iste circumstantias in un ren de normal grados de elasticitate quando le proportion del clearance de inulina al clearance de para-aminohippurato (le fraction de filtration) es elevate. Augmento del pression intra le glomerulo promoverea probabilemente le filtration de proteina, o directemente o per distender le poras intercellular.

In nostre experientia proteinuria esseva regularmente inducite in subjectos normal e in subjectos con proteinuria orthostatic in position jacente per le infusion intravenose de epinephrina e norepinephrina. Iste effecto esseva precedite per un marcate elevation del fraction de filtration. Grande augmentos del proteinuria esseva effectuate in patientes con nephritis chronic per le infusion intravenose de norepinephrina (vide graphico 2). Iste alteration se produceva parallel al alteration del fraction de filtration.

In orthostase il es le regula que vasoconstriction renal occurre con ben mantenite filtration glomerular e un resultante elevation del fraction de filtration. Iste schema de adjustamentos del hemodynamica renal con alterationes postural es apparentemente universal (vide graphico 1), excepte quando le ren es severmente ledite. Longe periodos de orthostase que resulta in fatiga o syncope orthostatic pote effectuar un reversion in ille schema, producente un reduction del filtration glomerular in proportion al usualmente sever grados de ischemia renal. Sub tal conditiones, orthostase non resulta in augmentos de proteinuria.

Le adjustamentos postural del hemodynamica intrarenal suffice a explicar le observate variationes in le proratas del excretion proteinic in position jacente e in position erecte. In casos de levissime morbo renal, le mesme mechanismo explica probabilemente le presentia de proteinuria in orthostase e su absentia in position jacente.

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CASE REPORTS

THROMBOTIC THROMBOCYTOPENIC PURPURA: REPORT OF A CASE WITH SOME UNUSUAL CHARACTERISTICS *

By José Báez-Villaseñor, M.D., F.A.C.P.,† and Kurt Ambrosius, M.D.,‡
Mexico, D. F.

Despite the fact that the first case of thrombotic thrombocytopenic purpura was described in 1925,[1] it was not until 1947 [2] that this disease was reported with any frequency. It has been said [2] that only 55 cases had been reported up to 1952.

Following is a description of a case which presented some rather unusual characteristics.

Case Report

A 43 year old married woman, resident of Mexico City, was admitted to the Hospital de Enfermedades de la Nutrición on May 26, 1954.

In 1946 she had begun to observe the frequent appearance of spontaneous or trauma-provoked cutaneous ecchymosis.

In 1948, six years before she was hospitalized, she had purpura with generalized cutaneous ecchymosis, petechiae and moderate epistaxis. These manifestations, together with pallor and asthenia, persisted for two months and then slowly and spontaneously disappeared. In 1949, one year later, another outbreak of purpura with the same characteristics occurred. Again in 1950, four years before hospitalization, the purpura recurred with greater intensity, and jaundice was also evident. Manifestations of acute anemia were present and blood transfusions were necessary. This third attack lasted for three months.

From then on the purpuric attacks were more common, of medium intensity and without jaundice. The last episode began on April 29, 1954, four weeks before the patient was admitted to the hospital. It was of considerable intensity. For the first time neuropsychiatric manifestations were present: paresthesias and hemiparesis of the left arm, aphasia, and a certain amount of disorientation with regard to time and space. (Because of this fact all data related to past history were verified with the patient's husband.)

At no time during the present illness was fever present.

In the physical examination it was found that the patient was disoriented and apathetic, and that her answers were inadequate and incongruent. She stuttered, her speech was dysarthric, and she was unable to carry out even the simplest mathematical problem.

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† Consultant in Clinical Hematology, Hospital de Enfermedades de la Nutrición, and Professor of Medicine (Clinical Hematology), Escuela de Medicina de la Universidad Nacional, México, D. F.

‡ Former Pathologist of the Hospital de Enfermedades de la Nutrición.

From the Department of Pathology, Hospital Infantil, México, D. F.

Requests for reprints should be addressed to José Báez-Villaseñor, M.D., Hospital de Enfermedades de la Nutrición, Calle del Dr. Jiménez 261, México 7, D. F., México.

Temperature was 36° C.; pulse, 96 per minute; blood pressure, 110/80 mm. of Hg. There was extreme pallor, with a subicteric tint in the conjunctivae. The eyegrounds showed small bilateral hemorrhages without edema. The cranial nerves were normal. Purpura of medium intensity, as evidenced by petechiae and generalized ecchymosis, was present, and was predominant on the upper extremities. Hypotonia was manifest, with loss of strength, especially in the left arm. There was lateralization of the reflexes to the left, with an abnormal plantar reflex on the same side. Adenopathy, liver enlargement and splenomegaly were not found.

Laboratory Data: Blood hemoglobin varied between 8.2 and 10.0 gm.%, with red cell counts between 2,500,000 and 3,200,000 per cubic millimeter. The anemia

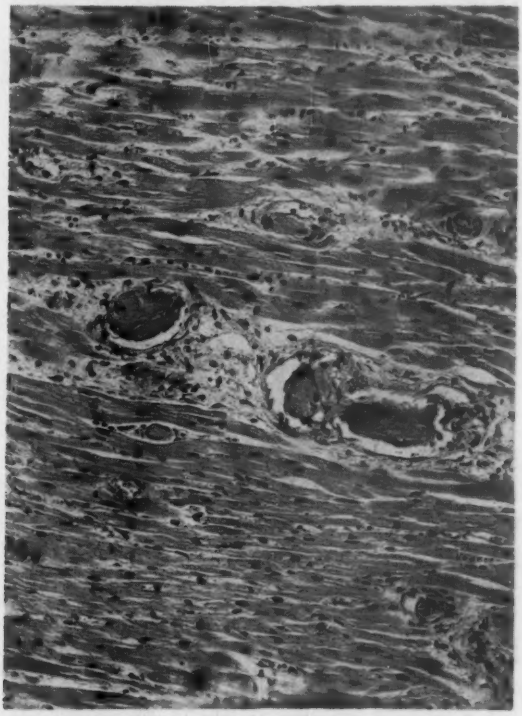


FIG. 1. Photomicrograph of myocardium showing some arterioles with thrombotic formations.

was always of the normochromic-normocytic type. Reticulocytes varied between 12 and 33%, and one to four normoblasts per 100 leukocytes were found. Microspherocytosis, anisocytosis and poikilocytosis were also present. The sedimentation rate was increased.

The white blood cell counts varied between 4,550 and 9,000 mm^3, with 71 to 78% neutrophils and increase in the immature forms, as there were 36% non-segmented neutrophils.

The platelet count was never above 44,000/mm^3, which coincided with the absence

of clot retraction, with a prolongation of the bleeding time and a positive tourniquet test, and without alterations of the coagulation time of the oxalated plasma when recalcified, or of the prothrombin time.

The bone marrow was very hyperplastic, with an erythrogranulocytic ratio of 1.4 to 1, and a considerable increase in megakaryocytes. There were 96% normoblasts. No relevant changes were seen in the white blood cell series.

Hypotonic fragility of red blood cells began at 0.60% and ended at 0.30%. In the control the figures were 0.50% and 0.30%.



FIG. 2. Myocardium. Photomicrograph (high power) which represents an arteriole with thin wall and a thrombus formation covered by endothelium and a narrow communication with the arteriole wall.

The hemolytic index was 49; the average fecal urobilinogen output per day was 169.3 mg.%; indirect plasma bilirubin oscillated between 0.25 and 0.56 mg.%, and no direct bilirubin was present in the blood. The Coombs' test was positive. Incomplete antibodies were found by means of trypsin-treated red cells and by the use of bovine albumin medium, with titers of 1:64 and 1:32, respectively.

Plasma globulins were 2.95 gm.%; blood urea varied from 180 to 340 mg.%; creatinine was 4.5 to 5.2; blood calcium was 8.26, and blood phosphorus was 8.9 mg.%. Urinalysis showed a low specific gravity (1.007 to 1.008), hematuria, albuminuria (0.50 to 0.65 gm.%), and hyaline and granular casts.

The following tests, reactions or examinations were normal or negative: liver function tests; cephalin cholesterol flocculation; thymol turbidity and flocculation; cold agglutinins; serologic reactions for syphilis; Weltmann's coagulation band; Paul-Bunnell test, and investigation of occult blood in stools.

Clinical Course: In spite of the lack of fever, the diagnosis of thrombotic thrombocytopenic purpura was advanced and a grave prognosis accepted. Cortisone was administered, as well as potassium chloride and a low sodium diet. The patient continued without important changes for the first three days. The temperature, recorded every eight hours, remained between 36° C. and 37° C.; the pulse around 80.



FIG. 3. Myocardium. Photomicrograph (high power) showing an arteriole with proliferation of the wall.

On the fourth day after admission the patient became comatose and died 48 hours later.

Pathologic Studies: At autopsy the body was found to be in a good state of nutrition, with extensive violet colored spots distributed irregularly on the skin of the face, arms, hands, thorax and legs. There was a subcutaneous hematoma in the right parietal region.

Punctate hemorrhages were found in the myocardium, endocardium, epicardium, gastric mucosa and adrenals. There were three superficial ulcers in the gastric mucosa. The liver weighed 1,780 gm. and the spleen 180 gm.

Microscopic arteriolar lesions were found in the following organs: myocardium (figure 1), spleen, stomach, pancreas, kidneys, adrenals and brain. They were not seen in the liver or lungs. These lesions consisted of small thrombotic formations, which were more abundant in the myocardium and spleen. Their morphology was not that generally seen in thrombi but seemed to consist of a proliferation of the intima and of the media of the arterioles. These formations communicated by a wide base with the arteriolar wall. In some places these connections were narrower, and in this case the thrombi had an elongated form (figures 2 and 3). Most of the thrombotic formations were covered by endothelium, or by a fine membrane which

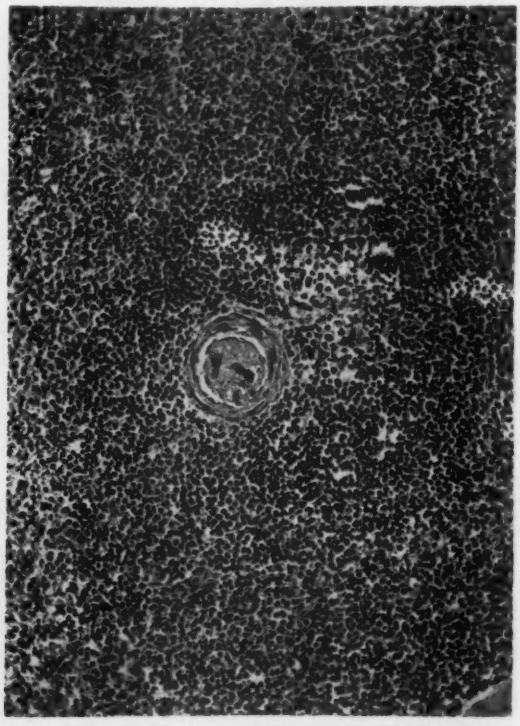


FIG. 4. Photomicrograph of spleen representing an arteriole with a thrombotic formation which occludes the lumen. This formation is covered by endothelium.

stained blue with the Schiff reagent (figure 4). Often they presented no structure and were eosinophilic, or else took a violet color with the Schiff dye. At other times it was observed that, included in the amorphous eosinophilic substance, there were relatively large and elongated nuclei which looked like endothelial cells (figures 5 and 6.).

An inflammatory reaction was not present in the wall of the arterioles or close to them. Hyalinization of the arterioles was found occasionally, with intimal proliferation but without thrombotic formation. The venules did not present alterations.

In the submucosa of the stomach, at the areas corresponding to the ulcerations,

the thrombotic alterations were also found. In the spleen and myocardium there was increased arteriolar proliferation, since at least 12 arterioles were found in one high power field.

The final pathologic diagnosis was thrombotic thrombocytopenic purpura with arteriolar alterations predominating in the myocardium, brain, spleen, stomach, pancreas, kidneys, adrenals and subcutaneous tissue, and with hemorrhages in the skin, myocardium, endocardium, pericardium, adrenals and mucosa of the gastrointestinal tract.

The vascular alterations and cerebral edema were suggested as the probable cause of death.

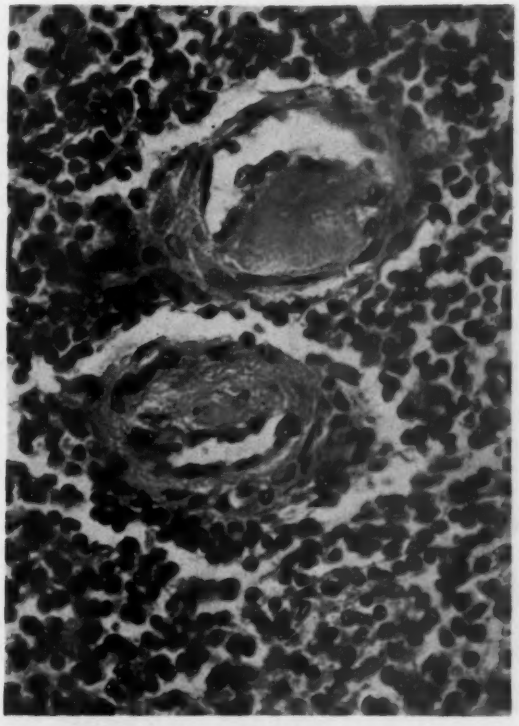


FIG. 5. Spleen. Photomicrograph (high power) of two arterioles, one of which shows enlargement of the wall by a hyaline mass. The other thrombus contains nuclear rests.

COMMENT

First, attention should be called to the clinical duration of this case. Singer has pointed out [2] that in only two cases in the literature reviewed by him was there a chronic course. In one of them, described by Meacham,[3] it was possible to prove, in an examination of the spleen removed three years before death, the presence of the typical alterations of thrombotic thrombocytopenic purpura. Adelson et al.,[4] in a review of 40 cases from the literature, mentioned that five

patients had a clinical course of from one to 10 years, but in some of them there was some doubt as to the correct diagnosis, or the actual duration of the thrombotic thrombocytopenic purpura.

In this case, the first purpuric manifestations occurred eight years before the death of the patient, and two years after its first occurrence the purpura was very extensive. The third attack of purpura, which took place in 1950—that is, about the middle of the clinical course of the disease—occurred with jaundice, which probably indicated that by this time the physiopathologic mechanisms of thrombotic thrombocytopenic purpura were already established. It is interesting to note that during the intervals the remissions were complete, and from this point of view in this case the thrombotic thrombocytopenic purpura can be considered as recurrent.

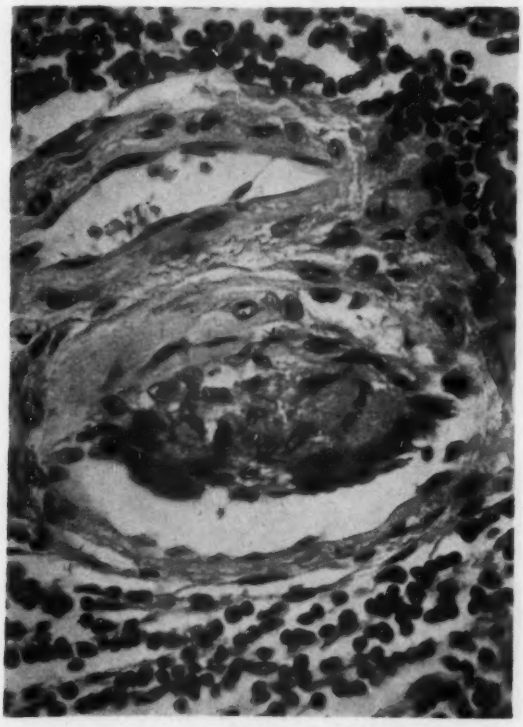


FIG. 6. Spleen. Photomicrograph (high power) which shows two arterioles with enlargement of the wall; one contains a thrombotic formation with some nuclei.

The second, and still more unusual abnormality in this case was the absence of fever. It is accepted [2] that fever is a characteristic symptom of this disease, and that in the final phase there is often hyperpyrexia. Two cases are mentioned in the literature [5, 6] in which fever was not present. In the present case fever was not observed at any time during the course of the disease, and during the final episode the hospital records demonstrate this absence of fever.

The third fact worthy of mention was the positive Coombs' test, which is ordinarily negative in thrombotic thrombocytopenic purpura. Few cases have been reported [7] in which the Coombs' test has been positive. As to the mechanism of such type of response, it is accepted that a positive Coombs' test suggests the possibility that the hemolysis is due to extra-erythrocytic factors, a possibility which in this patient is backed up by the presence of antibodies, as demonstrated by the results of the titration by means of trypsin-treated red cells and by the use of the bovine-albumin medium.

The other clinical and hematologic manifestations, as well as the pathologic alterations of this case, were those usually observed in cases of thrombotic thrombocytopenic purpura. So, in the final phase, the clinical picture was characterized by the association of thrombocytopenic purpura, hemolytic anemia, neuropsychiatric manifestations and the inefficiency of cortisone therapy. Accordingly, the laboratory data showed:

1. Evidence of erythrocyte destruction, as shown by the anemia, the hemolytic index, the microspherocytosis, and the increased osmotic fragility.
2. The presence of increased erythropoiesis, as indicated by the normoblastic hyperplasia of the bone marrow and the reticulocytosis and the normoblastemia.
3. The thrombocytopenic character of purpura, as demonstrated by the platelet count, the increase in the megakaryocytes of the bone marrow and the absence of clot retraction; the positive tourniquet test and the increased bleeding time were findings also corroborative of that type of purpura.

The pathologic alterations of this case were localized exclusively in the arterioles, without lesions of the venules, and the organs most affected were the myocardium, spleen, adrenals, pancreas, brain and kidneys. As observed in other cases, there were no pulmonary or hepatic alterations,[2] nor were inflammatory reactions found around the thrombosed vessels.

Summary

A case is presented of a 43 year old woman in whom the final diagnosis of thrombotic thrombocytopenic purpura was established. There were episodes of purpura for eight years, and the third one, which occurred six years before death, was accompanied by jaundice; the same association occurred in the final exacerbation, which, in addition, was characterized by the presence of neurologic manifestations.

Fever was not observed at any time during the course of the disease.

The laboratory findings demonstrated the thrombocytopenic nature of the purpura and the presence of hemolytic anemia, with microspherocytosis and a positive Coombs' test.

The postmortem examination showed the presence of arteriolar thrombotic formations in the myocardium, spleen, brain, stomach, pancreas, adrenals and subcutaneous tissue.

The chronicity of the disease, the absence of fever and the positive Coombs' test are mentioned as unusual findings in thrombotic thrombocytopenic purpura.

Acknowledgment

The authors wish to thank Dr. Carl V. Moore and Dr. Edmundo Rojas for their comments in this case.

SUMMARIO IN INTERLINGUA

Le autores presenta le caso de un femina de 43 annos de etate, originalmente residente a Mexico D. F., qui habeva episodios de purpura durante octo annos ante su morte. Le tertie tal epsodio, occurrente sex annos ante morte, esseva accompaniate de jalnessa. Le mesme association occurreva etiam in le ultime acerbation que esseva characterisate in plus per le presentia de manifestationes neurologic e psychiatric, incluse paresthesias, hemiparesis del bracio sinistre, aphasia, e un certe grado de disorientation mental. Febre non esseva observate a ulle tempore durante le curso del morbo. Le examine physic, executate durante le phase final quando le patiente esseva studiate al Hospital de Morbos de Nutrition, revelava que su temperatura esseva 36 C.

Le patiente exhibiva extreme grados de pallor, con un tinctura subicteric del conjunctivas. Le fundos ocular monstrava parve hemorrhagias sin edema. Le nervos cranial esseva normal. Purpura de intensitate medie, manifeste in petechias e ecchymosis generalisate, esseva presente predominantemente in le extremitates superior.

Hypotonia esseva evidente, con perdita de fortia, specialmente in le bracio sinistre. Se notava lateralisation del reflexos verso le sinistra, con un anormal reflexo plantar a ille mesme latere.

Adenopathia, allargamento hepatic, e splenomegalia non esseva constatate.

In despecto del absentia de febre, le diagnose de purpura thrombotic thrombocytopenic esseva proponite, e cortisona esseva administrate. Durante le prime tres dies, le patiente remaneva sin alterationes importante. Le temperatura, que esseva mesurate omne octo horas, esseva semper inter 36 e 37 C. Le quarte die post su admission al hospital, le patiente deveniva comatose e moriva 48 horas plus tarde.

Studios laboratorial revelava le natura thrombocytopenic del purpura e le presentia de anemia hemolytic, con microspherocytosis e positivitate in le test de Coombs.

Le examine necroptic monstrava le presentia de formationes arteriolo-thrombotic in myocardio, splen, cerebro, stomacho, pancreas, glandulas adrenal, e le histos subcutanee. Esseva notate hemorrhagias in le pelle, le corde, le adrenales, e le vias gastrointestinal. Alterationes vascular e edema cerebral esseva considerate como le causa del morte.

Le chronicitate del morbo, le absentia de febre, e le positivitate del test de Coombs es discutite como constatationes inusual in purpura thrombotic thrombocytopenic.

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BONE MARROW DEPRESSION SUCCESSFULLY TREATED WITH HYDROCORTISONE AND CORTICOTROPIN (ACTH) *

By JOHN F. MURRAY, M.D., *London, England,* S. FRED RABINER, M.D., *Long Island, New York,* and BERNARD KABAKOW, M.D., *New York, N. Y.*

CORTISONE, hydrocortisone, and adrencorticotropic hormone (ACTH) have been employed therapeutically in a variety of blood dyscrasias.[1] These compounds have been found particularly effective in thrombocytopenic purpura,[2] acquired hemolytic anemias [3] and, to a lesser extent, in acute leukemias.[4] Recently several reports have suggested that cortisone and ACTH are useful, and may perhaps be life-saving, in the treatment of drug-induced agranulocytosis.[5-9]

The following is a report of a patient with marked bone marrow depression, possibly secondary to propylthiouracil administration, who showed an initial response to intravenous hydrocortisone and was subsequently successfully treated with ACTH.

CASE REPORT

A 36 year old white unmarried typist came under observation on the fourth day of her illness following admission to the University Medical Service of Kings County Hospital for fever and sore throat. Approximately 10 months prior to admission the patient had noticed the onset of nervousness, slight exophthalmos, and an eight pound weight loss despite a good appetite. Her basal metabolic rate was found to be plus 37. She was given propylthiouracil (200 mg. daily). Her white blood cell count, determined every two weeks, was found to vary between 6,000 and 8,000 per cubic millimeter. After two months of treatment the patient discontinued therapy without medical advice and was asymptomatic for the next four months. Three months before admission, due to a recurrence of symptoms, the patient was advised to resume the original dose of propylthiouracil. A multivitamin preparation (Theragran) was also added. One month prior to admission the dosage was decreased to 100 mg. daily. Her leukocyte count was again checked every two weeks, the last count 10 days prior to admission, when it was 7,000 per cubic millimeter. Two days before admission the patient had the sudden onset of sore throat with pain on swallowing and fever of 103 to 104° F. She was treated with 10 tablets of Coricidin and 10 tablets of oral penicillin, 200,000 units each, without improvement.

The past history was negative for allergic manifestations. The patient had been in good health prior to the onset of thyrotoxicosis, except for an uneventful appendectomy at the age of 16.

She was found on admission to be acutely ill, with manifest difficulty in swallowing. Her temperature was 103° F.; pulse rate, 108 per minute; respiratory rate, 20 per minute; blood pressure, 130/75 mm. of Hg. The skin was warm and dry and without eruptions. There was slight exophthalmos. There was no lid lag or impairment of convergence. The entire pharynx was markedly injected; the tonsils were enlarged, and each was covered with a thick, confluent whitish membrane that was easily scraped from the underlying tonsil without its bleeding. The neck was

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From the Division of Hematology, Department of Medicine, State University of New York College of Medicine at New York City, Brooklyn, N. Y.

Requests for reprints should be addressed to Bernard Kabakow, M.D., Montefiore Hospital, 210th Street and Bainbridge Avenue, New York 67, N. Y.

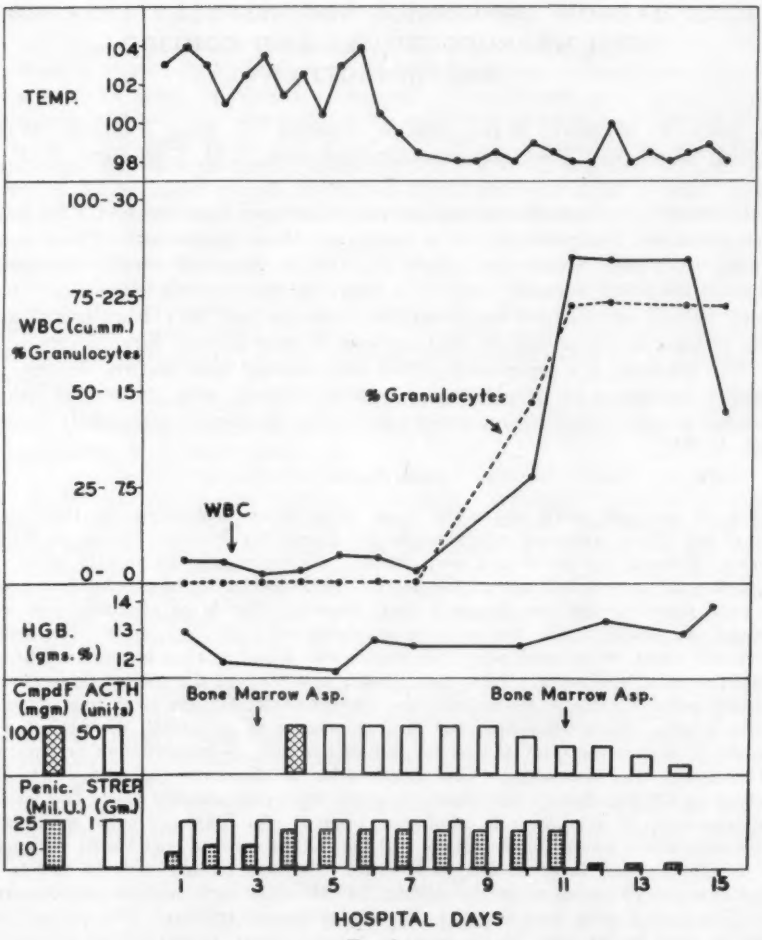


FIG. 1.

supple. Enlarged, tender submandibular glands were palpable bilaterally. The thyroid gland was enlarged to twice normal size. A small nodule was palpable in the right upper pole, where a bruit was heard. The lungs were clear. The heart was not enlarged, and there were no murmurs or abnormal sounds. The abdomen was negative except for a well-healed appendectomy scar. Pelvic examination was deferred, and rectal examination was negative. Neurologic examination was normal.

On admission the urinalysis was normal except for a trace of proteinuria. The hemoglobin concentration was 13 gm.%. Erythrocyte sedimentation rate was 46 mm./hour (Westergren). The white count was 1,800, with 100% lymphocytes. Chest x-ray showed slight increase in hilar markings. Mazzini test was negative. Throat culture grew *B. fecalis alkaligenes;* cultures for diphtheria and fungi were negative. Blood culture was sterile. Electrocardiogram on July 7, 1954, showed sinus tachycardia. A Rumpel-Leede test was negative. A sternal bone marrow

aspiration on the second hospital day produced a fatty, acellular film. A repeat sternal marrow puncture was performed the next day by Dr. R. Janet Watson, of the Department of Hematology; definite marrow spicules were observed, but on smear only an occasional lymphocyte, reticulum cell and fat were seen.

The patient's hospital course is depicted in figure 1. It can be seen that initially there was no response to large doses of antibiotics, and for the first three days in the hospital the patient continued to appear acutely ill, with marked temperature elevation. The leukocyte count had decreased to below 1,000 per cubic millimeter, and complete absence of granulocytes was noted on the peripheral blood smear.

On the fourth day hydrocortisone (100 mg.) was given intravenously over a six hour period. Thirty hours later the white cell count had increased from 650 to 1,850 per cubic millimeter (table 1), with 5% polymorphonuclear leukocytes in the differential count. Fifty units of ACTH were given intravenously, beginning on the fifth day, and were similarly administered on each of the next five days, with gradual reduction in dosage over the successive five days. The increase in the total leukocyte count and the granulocytosis that appeared following the ACTH therapy are shown in figure 1. After 10 days of hormone treatment the patient's white blood cell count had risen to 25,100 per cubic millimeter, with a differential count of 63% polymorphonuclear leukocytes, 4% bands, 4% myelocytes, 1% metamyelocytes, 21% lymphocytes and 7% monocytes. The hemoglobin had increased from 11.5 to

TABLE 1

Leukocyte Response Following Hydrocortisone Therapy

Time (hours)	W.B.C. per c.mm.	% Granulocytes	Absolute Granulocytes per c.mm.
0	650	1	6.5
2	850	Not determined	—
4	1,000	Not determined	—
6	950	Not determined	—
22	1,850	2	37.0
30	1,850	5	92.5

13.5 gm.%. A sternal bone marrow aspiration on the seventh day following institution of ACTH therapy revealed marked myeloid hyperplasia, with a myelocyte-erythrocyte ratio of 12.5:1. The patient showed a striking clinical remission within 24 hours of initiation of corticotropin therapy; her temperature fell from 103.6° to 98.6° F., she appeared less toxic, and the throat lesions began to improve objectively and subjectively.

Lugol's solution, 10 drops three times a day, was started one week after admission; three weeks later her basal metabolic rate was plus 12. One month after entry, under general anesthesia, a subtotal thyroidectomy was performed, with removal of a multinodular goiter. The patient's postoperative course was uneventful and she was discharged two weeks later, asymptomatic, and with a leukocyte count of 8,500 per cubic millimeter and a normal differential. The patient has been well since that time and, when last seen in the Hematology clinic, six months following discharge, was found to have a hemoglobin of 15.5 gm. and a white blood cell count of 8,850 per cubic millimeter, with a normal differential.

DISCUSSION

The case history is presented of a 36 year old female who was found to have fever, pharyngitis and toxicity associated with marked bone marrow hypoplasia

with severe leukopenia. After a suggestive leukocyte response to intravenous hydrocortisone, dramatic clinical and hematologic remission was produced by the administration of corticotropin over a 10 day period.

The bone marrow usually seen in acute agranulocytosis is not hypocellular and shows what appears to be a maturation arrest in the granulocyte series at the stem-cell or myeloblast stage.[10] The initial marrow in the case under discussion showed virtual aplasia, with only an occasional lymphocyte or reticulum cell visualized, and falls into Group I (aplastic anemia with aplastic marrow, with an extremely poor prognosis) of Rhoads and Miller.[11] The anemia in the patient was not striking, but the fall in hemoglobin from 13 to 11.5 gm.% was consistent with failure of erythropoiesis from the onset of illness, and if sufficient time had elapsed before the induced remission the anemia would probably have been progressive. In spite of the apparent absence of megakaryocytes in the marrow, platelets were seen on direct smear of the peripheral blood and no purpura or bleeding phenomena were seen. At the time of the original marrow puncture platelet precursors must have been present elsewhere in the patient's hematopoietic system, and it has been previously noted that hemorrhagic tendencies usually occur late in the course of aplastic anemia.

The drug responsible for the marrow depression cannot be definitely established; it is highly probable, however, that propylthiouracil, which is well known for its ability to produce agranulocytosis, is the causative factor. Rhoads and Miller [11] suggest that acute agranulocytosis and aplastic anemia may be related conditions, because both show a defect of maturation, and anemia usually supervenes if the agranulocytosis persists a sufficient length of time.

Adrenal steroids have been successfully administered in the treatment of drug-induced agranulocytosis, and appear to be useful in related bone marrow aplasia. It is conceivable that this patient might have survived with continued conservative management of antibiotics and supportive measures. However, the finding of a nearly acellular bone marrow with persistent leukopenia and falling hemoglobin seemed ominous prognostic signs.

The prompt elevation of total leukocytes, with slight increases in relative and absolute granulocyte count upon administration of intravenous hydrocortisone, encouraged further steroid therapy for prolonged effect. The subsequent persistent rise in white blood cells following intravenous ACTH therapy on 10 successive days is strongly suggestive that hormone administration was the determining factor in producing the rapid hematologic and clinical remission.

The mechanism by which ACTH and cortisone ameliorate granulocytopenia is unknown. These hormones have been shown to produce a sustained granulopoiesis in normal persons,[12] and would appear to have a similar effect in marrow depression. More recently, a leuko-agglutinin has been described as an etiologic factor in granulocytopenia; [13] in this variety, hormone therapy may alter the antigen-antibody reaction in a manner similar to that assumed to be effective in other immunologic blood disorders, such as some varieties of primary thrombocytopenic purpura and acquired hemolytic anemia. It is possible, although less likely, that the adrenal steroids may have a direct neutralizing chemical action on the offending drug and thereby relieve its toxic effect of suppression of the bone marrow.

Summary

A case is presented of bone marrow depression, possibly induced by propylthiouracil, and successfully treated with hydrocortisone and corticotropin. The mechanisms by which steroid therapy may favorably influence bone marrow depression are discussed. These hormones appear to be indicated in drug-induced marrow depression or granulocytopenia.

Summario in Interlingua

Es presentate un caso de granulocytopenia inducite per propylthiouracil e tractate a bon successo con hydrocortisona. Le patiente, un 36-enne non-maritate dactylographa de racia blanc, habeva recipite durante un periodo de 10 menses ante su admission al hospital un curso intermittente de 200 mg de propylthiouracil per die como tractamento indicate post un diagnose de hyperthyroidismo. Illa esseva admittite al Hospital de Kings County (New York) con febre e mal de gurgite como major gravamines. Il esseva constatate que illa habeva agranulocytosis con hypoplastia del medulla ossee.

Le tractamento con hydrocortisona e plus tarde con ACTH resultava in un recuperation complete. Le observation consecutori al clinica hematologic esseva continuate durante sex menses. Le stato del patiente ha remanite bon.

Es discutite le mechanismos per que le therapia steroide pote exercer un influentia favorabile super le depression del medulla ossee. Il pare que iste hormones es indicate in casos de agranulocytosis a induction medicamentose.

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FUADIN THERAPY OF SCHISTOSOMIASIS ASSOCIATED WITH VENTRICULAR TACHYCARDIA AND DEATH: A CASE REPORT *

By ROBERT SCHICK, M.D., *Glenn Dale, Maryland,* ARNOLD B. RITTERBAND, M.D., *New York, N. Y.,* and AMOS H. LIEBERMAN, M.D., *San Francisco, California*

THE heavy influx of Puerto Rican immigrants into the United States during the last 15 years has focused increasing attention on the therapy of parasitic infestations. Schistosomiasis constitutes a particular problem because it may be associated with portal cirrhosis, splenomegaly with hypersplenism, and esophageal varices. The schistosomal parasite may have an astonishing longevity. Viable ova have been reported [1] in the rectal mucosa of patients as long as 25 to 30 years after they have left areas endemic for schistosomiasis with no possibility of reinfection.

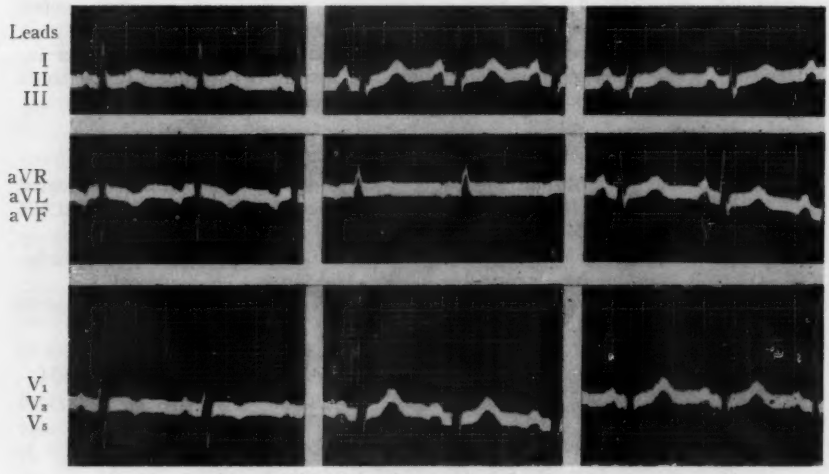


FIG. 1. Electrocardiogram before treatment.

In view of the increasing use of the organic antimony compound Fuadin in the therapy of schistosomiasis, we have been prompted to report this case of schistosomal cirrhosis in which Fuadin therapy appeared to be responsible for the development of ventricular tachycardia and death of the patient.

CASE REPORT

A 36 year old Puerto Rican housewife who had been in the United States since 1945 was referred to the Mount Sinai Hospital in July, 1954. During the preceding

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From the Medical Service of The Mount Sinai Hospital.
Requests for reprints should be addressed to Robert Schick, M.D., Glenn Dale Hospital, Glenn Dale, Md.

seven or eight months the patient had noted some weakness, a poor appetite, occasional low grade fever, and pains in the shoulders and knees. The symptoms were rather mild and somewhat vague, and in recent months had disappeared. In April, 1954, because of itching in the anus and perianal region, the patient was seen in the Tropical Disease Clinic of the Out-Patient Department, where the diagnosis of schistosomiasis was made after stool examination, and she was referred to the Hospital for therapy. There was no past history of heart disease, or of symptoms referable to the cardiovascular system.

Physical examination was entirely within normal limits except for the presence of a smooth, sharp-edged liver palpable 5 cm. beneath the costal margin. The spleen was not felt.

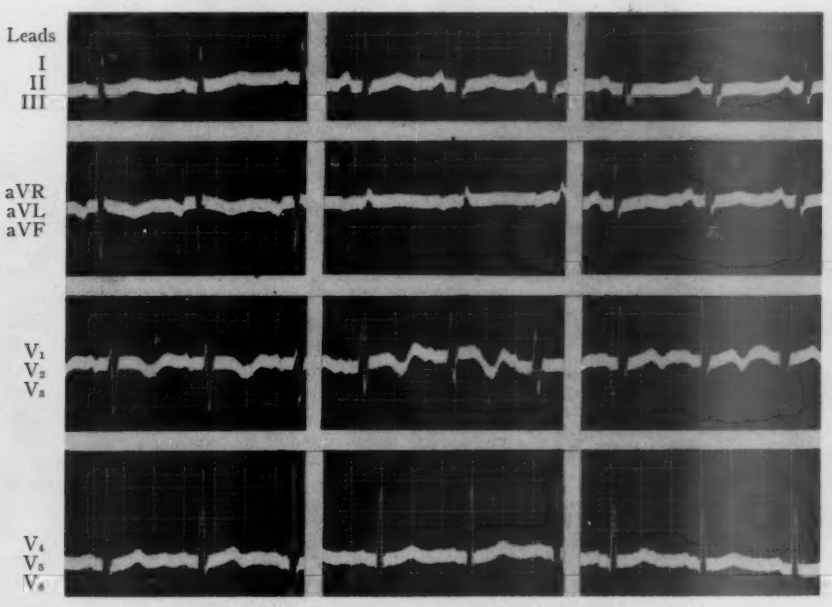


FIG. 2. Electrocardiogram on seventh day of therapy. Total dosage thus far, 35 c.c. of Fuadin.

The laboratory findings on admission included a hemoglobin of 12 gm. per 100 ml. The leukocyte count was 5,400 per cubic millimeter, with a normal differential count. Urinalysis was normal. Liver function studies were all within normal limits except for a slightly increased bromsulphalein retention of 10% in 45 minutes. The sedimentation rate (Westergren) was 14 mm. in one hour. A chest film was negative, and an electrocardiogram prior to therapy (figure 1) showed no abnormality.

Following these baseline studies the patient was started on Fuadin therapy, 5 c.c. (42.5 mg. trivalent antimony) intramuscularly daily. On the second day of therapy papular lesions appeared on the shoulders and back, and later over the face and arms. There was no associated itching. The patient was seen by a dermatologic consultant, who suggested that she had pityriasis rosea. The rash was treated with pyribenzamine, with some fading. On the seventh day of Fuadin therapy an electrocardiogram (figure 2) showed flattening of the T waves. The patient remained

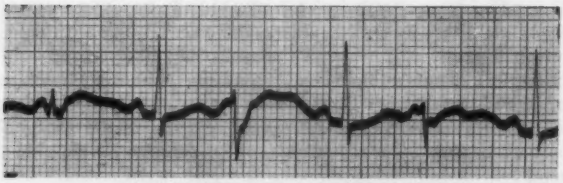


FIG. 3. Lead II. Multifocal ventricular premature contractions.

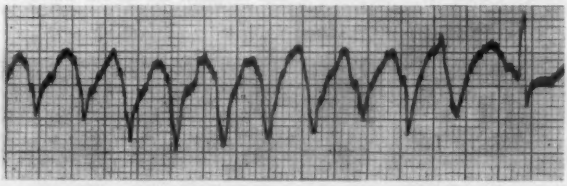


FIG. 4. Lead II. Burst of ventricular tachycardia.

asymptomatic and entirely well. There was a mild sinus tachycardia, with pulse rates up to 100. On the fifteenth day the patient developed conjunctival burning, itching of the skin and some arthralgias. That night she complained of some epigastric distress. The following day she refused her Fuadin. She complained of joint pains, had a nonproductive cough and was restless and emotionally disturbed. She received a total of 75 c.c. of Fuadin intramuscularly in 15 days. She complained of "jumping in the stomach," and was found to be diaphoretic and had an irregular pulse. Blood pressure was 120/60 mm. of Hg. The patient suddenly lost consciousness and became cyanotic, with absent pulse and blood pressure, and with cessation of breathing. Artificial respiration was administered, and 100 mg. of Pronestyl were injected intravenously, as it was thought that ventricular fibrillation was likely in view of the previously noted irregular pulse. The patient showed a rapid clinical recovery, and an electrocardiogram taken immediately after the attack revealed a regular sinus tachycardia of 120, with ST segment depressions and the previously noted T wave changes. Four and one-half cubic centimeters of a 10% solution of Dimercaprol (BAL) were given intramuscularly. A few minutes later the patient had another episode of unconsciousness, with cyanosis and seizures. A continuous electrocardiogram recorded the presence of multiple ventricular premature contractions, and then ventricular tachycardia (figures 3 and 4). For the next three minutes the patient continued comatose and cyanotic. Six hundred milligrams of Pronestyl were injected very slowly intravenously, until conversion to regular sinus rhythm took place, at which point the injection was discontinued. The electrocardiogram then revealed regular sinus rhythm with depressed S-T segments ("insufficiency pattern"). A few minutes later another episode of ventricular tachy-

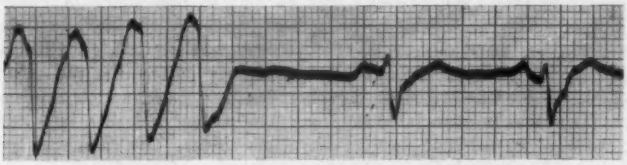


FIG. 5. Conversion of ventricular tachycardia to regular sinus rhythm by intravenous Pronestyl.

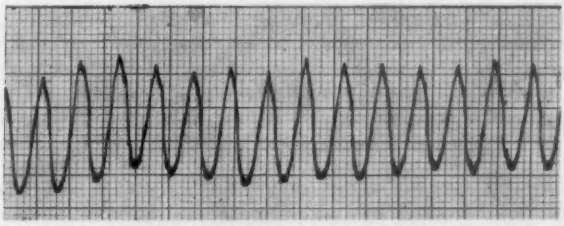


FIG. 6. Lead II. Ventricular tachycardia with clinical picture of vascular collapse.

cardia supervened, again accompanied by cyanosis and convulsions. This also was terminated by a slow injection of Pronestyl intravenously. A tracing taken after conversion to RSR rhythm revealed the presence for the first time of a widened QRS complex, which was assumed to represent interventricular conduction disturbance, secondary to Pronestyl (figure 5).

During the next several hours the patient had frequent bouts of ventricular tachycardia (figure 6), usually associated with hypotension and unconsciousness. Prolonged bouts were terminated by slow intravenous injection of Pronestyl, and at one point 0.6 gm. of quinidine hydrochloride was given intramuscularly. Approximately three and one-half hours after the beginning of the bouts a drop in blood pressure to 50/0 mm. of Hg was noted. This was promptly corrected by a slow infusion of noradrenaline (Levophed).

The patient continued to have many bouts of ventricular tachycardia and frequent

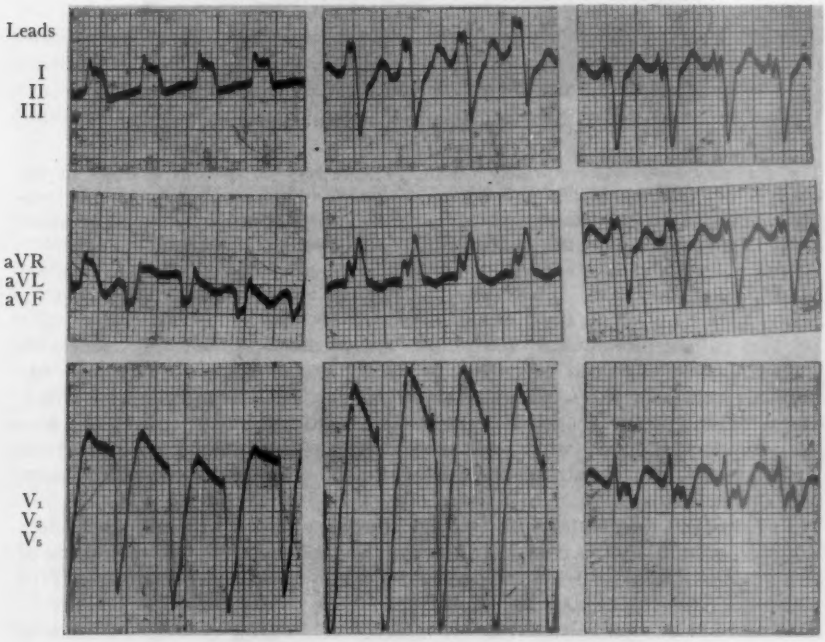


FIG. 7. Left bundle branch block.

multifocal ventricular contractions. Because of the marked QRS widening found during periods of regular sinus rhythm, it was decided to avoid further use of Pronestyl if possible. However, several times after prolonged bouts of tachycardia accompanied by coma and cyanosis small amounts of Pronestyl had to be administered until conversion took place. A complete electrocardiogram taken some 10 hours after the onset of arrhythmias showed a left bundle branch block pattern (figure 7).

During the next four hours the patient did fairly well with maintenance of basically RSR. No Pronestyl was administered. In the early morning, 14 hours after the onset of the bouts of tachycardia, the patient again suddenly lost consciousness and became cyanotic. The electrocardiogram recorded a rapid ventricular tachycardia. After some four to five minutes of observation, during which time the patient remained cyanotic and convulsing, with absent blood pressure, a slow infusion of 200 to 250 mg. of Pronestyl was finally given as a measure of desperation. The patient promptly reverted to regular rhythm but with extreme widening of the QRS complexes (figure 8), and she died soon after; she had received a total of some 3.2 gm. of Pronestyl intravenously.

Postmortem examination revealed an enlarged, finely granular liver, which on microscopic examination revealed mild cirrhosis, with a small number of schistosomal ova granulomata. The spleen was unremarkable. The heart was of normal size.

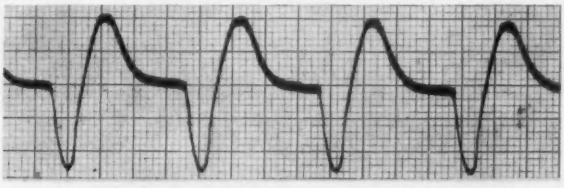


FIG. 8. Lead II. Preterminal electrocardiogram.

The coronary arteries were widely patent. There were no obvious changes in the heart muscle, and specifically no evidence of muscle degeneration. A fat stain was negative. The lungs revealed an early focal bronchopneumonia in the right lower lobe. The remaining organs, including the brain, were unremarkable.

COMMENT

This patient presented several of the "toxic" manifestations associated with Fuadin therapy in a large percentage of cases. In retrospect, the skin rash was probably secondary to Fuadin, as were the arthralgias and conjunctival burning. In the absence of any evidence of organic heart disease in this patient, the presumption is strong that Fuadin was responsible for the development of ventricular tachycardia, with its attendant episodes of cardiovascular collapse with Adams-Stokes seizures.

This patient was treated with a dosage schedule of 75 c.c. of Fuadin in 15 days (usual course, 40 to 45 c.c. in 17 to 19 days) as part of a study on the relation of dosage and rapidity of treatment to relapse rate. Most et al.[26] have advocated treatment schedules of 100 c.c. in 20 days.

Pronestyl was administered slowly intravenously during prolonged periods of ventricular tachycardia, with prompt conversion to sinus rhythm and temporary

clinical recovery. This appeared to be a life-saving measure. Eventually, evidence of Pronestyl toxicity in the form of widened QRS complexes was noted, and thereafter an attempt was made to withhold further Pronestyl. However, prolonged periods of collapse, during which the patient was cyanotic, convulsing and apneic, forced resumption of Pronestyl from time to time, again with reversion to sinus rhythm, with clinical recovery but with more pronounced evidences of Pronestyl toxicity.

During the patient's last episode of ventricular tachycardia, which was of four to five minutes' duration, Pronestyl was withheld, and was finally administered intravenously in small doses when death appeared inevitable. The patient promptly reverted to regular rhythm, but with extreme widening of the QRS complexes, and then died.

No conclusions can be drawn regarding the efficacy of BAL, since only one injection of 4.5 c.c. was given. Spingarn and Edelman [25] reported on the use of short courses of BAL in three cases of Fuadin toxicity, in two of which the drug seemed to be of value. In none of the cases was there any noticeable effect by BAL on the electrocardiographic changes (T-wave inversions) induced by Fuadin. It should be noted that the results of experimental work in animals regarding the efficacy of BAL in organic antimony poisoning are conflicting. Braun et al.[2] found that the administration of BAL increased the tolerance of rabbits to lethal doses of compounds of antimony (including both Fuadin and tartar emetic) by more than 50%. Eagle et al.[3] reported a similar protective action of BAL in rabbits given lethal doses of organic antimonials. These authors also found that BAL significantly increased the urinary excretion of antimonial compounds. Gamill et al.,[4] on the other hand, concluded from their studies that BAL significantly reduced the mortality rate of rats receiving single or repeated doses of tartar emetic, but that the lethal effect of Fuadin was clearly enhanced by the administration of BAL.

Discussion

In 1915 McDonagh introduced an intravenous antimonial, tartar emetic. In 1918 he and Christophensen demonstrated its value in the treatment of schistosomiasis. Since then it has been agreed that the antimonial compounds are the treatment of choice in this disease. In 1930 Khalil Bey and Betache developed a new compound, Fuadin, and claimed a lesser toxicity for this drug than with tartar emetic. Other antimonial drugs have been tried since in a search for a less toxic agent. Only the trivalent antimonials have therapeutic efficacy in schistosomiasis.

Fuadin is sodium antimony bis-catechol-2,4-disulfonate, and is also referred to as Stibophen. It contains 13.6% of trivalent antimony. One cubic centimeter of a 6.3% solution, the form in which the compound is marketed in the United States, represents 8.5 mg. of trivalent antimony.

Administration, Distribution, Excretion

The antimonial compounds are administered parenterally, tartar emetic is administered intravenously, and Fuadin intramuscularly. Bartter [5] found that, in man, 30 minutes after an intravenous injection of radiotartar emetic, only 5 to 20% of the theoretic initial blood level remained. At the end of 12 hours this

level was only 1%. There is a rapid shift of the trivalent antimony from the plasma to the red blood cells, with significantly higher concentrations thereafter in the red blood cells.[6] Evidence has been presented to show that the antimony is attached to the globin part of the hemoglobin in the red blood cells.[7]

The antimony is distributed among all the body tissues, but by far the greatest amount is concentrated in the liver;[8] a lesser quantity is found in the spleen and kidneys, and only a slight amount in the heart, lungs, brain and muscle,[9] even after multiple injections of either Fuadin or tartar emetic. In a course of antimonial therapy there is a slow accumulation of the drug in all the tissues of the body.[9, 10] However, several observers have found no evidence of more than slight accumulation in any body organ but the liver.[10, 11] Lippincott[11] showed that during a course of antimony therapy the blood levels, taken just prior to injection of the subsequent dose, rose to a peak level of 100 μg/L., where a plateau was reached near the end of therapy. On cessation of therapy the blood levels fell only gradually, and at the end of 100 days as much as 7 μg/L. were still found.

Antimony is excreted from the body by the urine and feces. Bartter[5] reviewed the literature and confirmed the fact that 80 to 90% of the antimony is excreted via the kidney in man. After a single dose of tartar emetic only 12% is excreted in the succeeding 24 hour period, and only 30% by the end of a week. As with digitalis, body and blood levels increase, and the percentage of a dose excreted in the succeeding 48 hour period rises. Thus, by the end of a course of Fuadin therapy, as much as 55% of the preceding dose may be excreted in this time.

Toxicity

In acute toxicity antimony is much like arsenic, causing bowel irritation, severe emesis and possible vascular collapse. Cases of sudden death have been reported too (vide infra).

Pesigan,[12] using a 40 c.c. course only of Fuadin, still found that 63% of 1,135 cases had some reaction. The most frequent was a combination of anorexia, nausea and vomiting, occurring in 48%. Weakness was found in 30%, headaches in 30%, arthralgias in 22%, fever in 16%, and skin rashes in 11.4%. Other symptoms of lesser frequency included dizziness, abdominal pains, cough, muscle pains, bloody bowel movements and itching. One case had a substernal constricting pain. This has also been reported by others.[13, 14] Others have noted conjunctivitis, orbital pains, fainting, dyspnea, facial edema and headache.[15] Jaundice is rarely seen. A reaction consisting of urticaria, husky voice and collapse, occurring after the sixth or seventh injection in a course of therapy, has been described.[15]

Most of the cases in Pesigan's series[12] developed their initial reaction after the third or fourth injection, 50% occurring at these times, with only a decreasingly small number occurring thereafter. In this series he found that 35% of the cases that developed reactions had spontaneous subsidence of these reactions while Fuadin therapy was continued. He did not consider that any of the reactions that occurred were contraindications to continuing therapy.

Most observers agree that severe renal disease, advanced liver disease and cardiac disease are contraindications to antimonial therapy. Pesigan[16] showed that, in cases of liver disease due to *Schistosoma japonicum*, therapy with Fuadin seemed to have improved the state of the liver, as measured by liver function

tests, particularly in patients treated in the early stages of liver disease, and only slightly or not at all in late stages of liver involvement. He did not find any aggravation of existing conditions of the liver in these severe cases.

Electrocardiographic Changes

In the last 20 years numerous observers have described significant changes in the electrocardiograms of the majority of patients receiving trivalent antimony therapy for schistosomiasis. Although the significance of these changes is not fully agreed upon, the changes themselves are fairly uniform and probably are due to the effect of antimony itself, as they occur with either tartar emetic, Fuadin or Anthiomaline.[17, 18, 19]

For the most part, the changes described are confined to the T waves, ranging from a simple decrease in amplitude to sharp inversion and even cove-planing of the T waves.[18, 19, 20] Such changes are reported to occur in 60 to 99% of patients receiving trivalent antimonials. Approximately 20 to 50% are reported by some workers [18, 19] to have a prolongation of the Q-T interval, and a significant number of patients show a fusion of the S-T segment with the T wave, so that the two may become indistinguishable.[18] Changes in the QRS complex have not been noted, and although a bradycardia was first described in patients undergoing antimonial therapy,[21] subsequent and more extensive studies did not reveal changes in rate that were significant.[17, 18, 19, 20]

Other changes of minor nature and not uniformly recorded include slight increase in P wave amplitude in 11% of patients,[18] slight prolongation in the P-R interval in some,[19] and occasional S-T segment depressions or elevations.[18] Apart from the T wave changes mentioned above, however, other reported changes are inconstant and variable.

Of interest in connection with the present case is the finding of infrequent ventricular premature contractions in two cases, and an A-V nodal rhythm in one case reported by Tarr.[19] In his excellent paper describing electrocardiographic changes in 141 cases receiving antimonial therapy, he noted that these few rhythm disturbances were not present before therapy and disappeared after therapy was stopped.

It has been noticed that, although electrocardiographic alterations occur with all trivalent antimonial preparations currently used,[17, 18] tartar emetic appears to produce these changes most readily.[19] The dosage of antimony required to produce such changes is extremely variable, as little as 10 c.c. of Fuadin producing alterations in some instances.[19, 20] In most cases the greater the daily or total dose of antimony used, the greater the T wave abnormalities.[18] There seems to be little if any correlation between electrocardiographic findings and such minor toxic symptoms as cough, nausea or arthralgia.[19] The persistence of the electrocardiographic changes produced is likewise variable, and may last more than two months after therapy has been stopped.[18] In a few instances the electrocardiographic changes may become more pronounced in the few days following the cessation of therapy and thereafter regress toward normal, but in most cases the changes start to revert toward normal one week after therapy has been stopped.[19]

As mentioned earlier, the significance of the electrocardiographic changes is not agreed upon, the majority of observers feeling that they are not indicative of cardiac disease or dysfunction. Mainzer and Krause,[21] however, feel that such

changes are indicative of toxic cardiac effects resulting from antimony administration. They believe that the electrocardiographic alterations produced by antimony result from intoxication of the heart muscle which, though not clinically evident in most cases, may result in sudden death. They related the electrocardiographic changes to those occasional cases of sudden death that occur either during or upon completion of a course of antimony therapy where postmortem findings are unrevealing. They described a case of sudden death occurring in a 28 year old man at the end of a course of Fuadin therapy in which he received 35 c.c. of Fuadin in 14 days.

Khalil [22] estimates that 0.2% of patients die suddenly during treatment for schistosomiasis, and that death generally occurs during the later phase of the course of therapy. He further states that most of these cases are never reported in Egypt because of the difficulty in obtaining postmortem examinations. He describes several cases of sudden death: one, a patient who suddenly collapsed and died after receiving his eighth injection of tartar emetic; another, a patient who had received 11 injections and died suddenly; a third, a nine year old boy who died suddenly after eight injections of Fuadin, and whose postmortem examination gave negative findings.

Alves [28] reports another case of sudden death in a native female who died in her sleep five days after her course of antimonial therapy had been completed. Here again, postmortem examination failed to show a cause of death.

Recently Cleve [14] reported three cases in which an alarming but reversible "toxic myocarditis" developed while the patients were on tartar emetic therapy. Also, the apparently increased incidence of sudden death in workers exposed to antimony in industry, as reported by Brieger et al.,[24] gives further credence to the belief that antimonials may be toxic to the myocardium.

It should be mentioned that, although cases of sudden death are described in the literature, they are certainly rare in comparison to the great numbers of patients who receive antimonial therapy without ill effect. Of the cases of sudden death described we could find none that had electrocardiographic studies, and it was only surmised that death was due to cardiac cause. Our case, with its accompanying electrocardiograms, suggests the manner in which antimony may cause sudden death.

Summary and Conclusions

A case is reported of ventricular tachycardia and sudden death occurring in a young patient being treated with Fuadin for schistosomiasis. The pharmacology and toxicity of Fuadin are briefly reviewed.

Fuadin therapy is unquestionably associated with a significant although small mortality.

In view of these facts, we would urge caution in the administration of Fuadin, with particular attention to signs and symptoms suggesting cardiac toxicity. The question as to whether all patients with schistosomiasis, particularly those in nonendemic areas, should be treated, might legitimately be raised.

Acknowledgment

The authors acknowledge with thanks the help of Dr. Clifford Spingarn in the preparation of this paper.

SUMMARIO IN INTERLINGUA

Existe reportos de morte subitanee occurrente in patientes qui recipeva compositos de antimonio trivalente in le curso del tractamento pro schistosomiasis, sed le mechanismos possibile de tal mortes ha nunquam essite elucidate. Viste le crescente uso de Fuadina in le therapia de schistosomiasis, nos nos senti urgite a reportar un caso de cirrhosis schistosomal in que therapia a Fuadina pareva esser responsabile pro le disveloppamento de tachycardia ventricular e pro le morte del patiente.

Le patiente esseva un menagera portorichese de 36 annos de etate, admittite al Hospital Monte Sinai de New York pro le tractamento de schistosomiasis. Esseva prescribite un curso de 20 dies de Fuadina intramuscular, in doses diurne de 5 cm³ (= 42,5 mg de antimonio trivalente). Post que le patiente habeva recipite un quantitate total de 75 cm³ de Fuadina intramuscular in le curso de 15 dies, illa subitemente perdeva conscientia, suffreva convulsiones, e deveniva cyanotic, con absentia de pulso e pression sanguinee. Illa experientiava un rapide restablimento clinic post un injection intravenose de Pronestyl, sed brevemente plus tarde illa habeva un simile attacco. A iste tempore un electrocardiogramma monstrava un alte frequentia de prematur contractiones ventricular e postea tachycardia ventricular. Illa de novo respondeva a Pronestyl intravenose. In le curso del sequente 14 horas illa habeva numerose episodios de tachycardia ventricular, usualmente associate con hypotension e perdita de conscientia. Inter iste episodios de tachycardia ventricular, le electrocardiogramma exhibiva signos de toxicitate a Pronestyl, con allargamento del complexos de QRS e plus tarde le configuration characteristic de bloco de branca sinistre, sed le essayo de abstraher le Pronestyl resultava in prolongate e indomabile episodios de tachycardia ventricular. Dece-quatro horas post le comenciamento de iste attaccos le patiente moriva.

Le examine necroptic revelava un corde que esseva perfectemente normal, tanto macro- como etiam microscopicamente. Le patiente habeva un leve cirrhosis del hepate, con un parve numero de schistosomal ovos granulomate. Le pulmones monstrava comenciante bronchopneumonia focal in le lobo dextero-inferior. Le altere organos, incluse le cerebro, esseva sin aspectos inusual.

In le curso del passate 20 annos, numerose autores ha describite frappante alterationes electrocardiographic in le majoritate del patientes recipiente compositos de antimonio trivalente. Iste alterationes es limitate in alte mesura al undas T, e le signification de illos non es completemente comprendite. Etiam le patiente del presente reporto monstrava ille alterationes del unda T ante que le prime signos de toxicitate cardiac deveniva evidente. Un revista de iste constatationes electrocardiographic es presentate, insimul con un discussion del pharmacologia del compositos de antimonio trivalente.

Le therapia a Fuadina es inquestionabilemente associate con un mortalitate de basse sed nonobstante significative grados. In vista de iste factos nos recommenda attention in le administration de Fuadina, specialmente con referentia a signos e symptomas que indica toxicitate cardiac.

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CONSTRICTIVE PERICARDITIS AS SEQUEL TO HEMOPERICARDIUM: REPORT OF A CASE FOLLOWING ANTICOAGULANT THERAPY *

By MAURICE H. LASZLO, M.D., *New York, N. Y.*

THE various causes of constrictive pericarditis have as yet not been thoroughly elucidated. Indeed, there is a wide divergence in various studies with respect to the incidence of the several known etiologic factors.[1–4] Undoubtedly tuberculous pericarditis is a fairly common precursor of constrictive pericarditis; pyogenic agents, polyserositis and previous nonspecific acute pericarditis are also at times implicated as causative factors. In addition, there still remains a large group of cases of indeterminate cause where the pathology of the pericardium, as found at surgery or autopsy, throws no light on the etiology. For example, no etiologic agent could be demonstrated in 57.7% of Chambliss' 61 operated cases, even after microscopic study of the pericardium.[3]

The following report is of interest in that constrictive pericarditis apparently developed from hemopericardium following anticoagulant therapy. This case thus affords additional clinical evidence in support of the etiologic importance of hemopericardium in the development of constrictive pericarditis.

CASE REPORT

A 41 year old white American seaman was admitted to the hospital on July 7, 1954, because of severe, viselike substernal pain of 12 hours' duration, associated with dyspnea, diaphoresis, nausea and vomiting, and not relieved by nitroglycerin. The past history was significant in that the patient had had occasional episodes of precordial pain on exertion, usually relieved by rest or nitroglycerin. He denied having had dyspnea on exertion, orthopnea or ankle edema. There was no hypertensive or diabetic background. There was no history of rheumatic fever or tuberculosis, or known exposure to it. The family history was noncontributory.

On admission the blood pressure was 160/80 mm. of Hg; pulse, 60 per minute; temperature, 99° F.; respirations, 30 per minute. The patient was a well developed, well nourished white male who appeared acutely ill. His skin was cool and moist; there was no cyanosis or neck vein distention. The lung fields were clear to auscul-

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Requests for reprints should be addressed to Maurice H. Laszlo, M. D., Montefiore Hospital, New York 67, N. Y.

tation. The heart border was percussed within normal limits; there was regular sinus rhythm. The sounds were strong, and no murmurs were heard. No organs were palpable in the abdomen. The remainder of the physical examination was not remarkable.

Admission white blood cell count was 15,500, with 72% neutrophils, 25% lymphocytes and 3% eosinophils. The hemoglobin was 14.9 gm. per 100 c.c. The hematocrit was 46% and the sedimentation rate was 43 mm. per hour (Wintrobe). A roentgenogram of the chest taken on the day of admission showed the heart to be of normal size and contour (figure 1). An electrocardiogram taken the same day disclosed regular sinus rhythm, with flattening of the T waves in the standard and

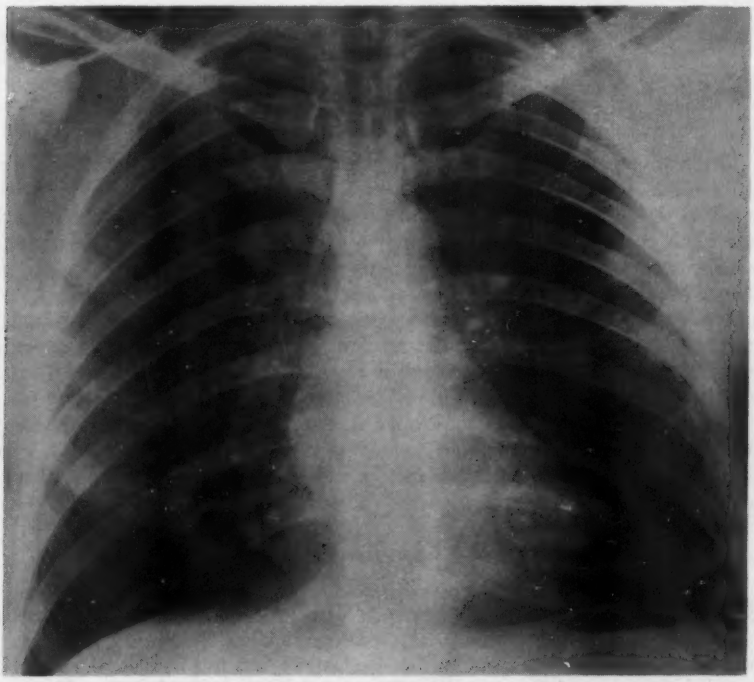


FIG. 1. Postero-anterior chest roentgenogram on admission, showing the heart to be within normal limits, size and contour. The lungs and pleural spaces are clear.

unipolar limb leads and in $V_{5, 6}$. There was slight depression of the S-T segment in V_{1-3}, with a marked depression in V_4 (figure 2, July 7). A repeat tracing taken the day following admission (figure 2, July 8) showed no marked change other than the return of the S-T segment in V_4 to the baseline. These findings were interpreted as indicative of generalized myocardial ischemia with coronary insufficiency. The possibility of lateral wall myocardial infarction was considered. The tracings were in no way suggestive of pericarditis.

Treatment consisted of bed-rest, oxygen, sedation and narcotics; anticoagulant therapy was instituted. He was given bishydroxycoumarin (Dicumarol), and his prothrombin time was maintained at approximately 20% of normal levels by the

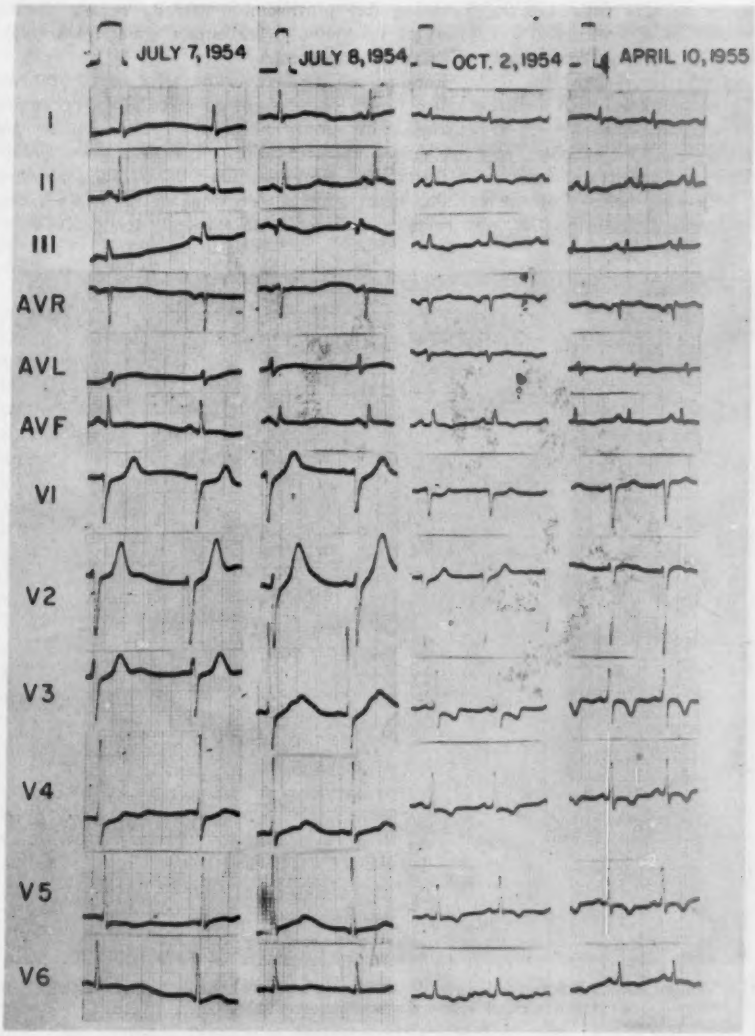


FIG. 2. *July 7, 1954.* Tracing shows flattened or diphasic T waves in standard and unipolar limb leads and over left precordium, with depression of S-T segments in V_{1-4}. *July 8, 1954.* S-T segment in V_4 is now iso-electric. Pattern is suggestive of lateral wall myocardial infarction. *October 2, 1954.* Note marked diminution in voltage in all leads, with evidence of digitalis effect and myocardial ischemia. *April 10, 1955.* Postoperatively, note increase in voltage in all leads. Digitalis was discontinued one month prior to this tracing.

Quick method (patient's prothrombin time, 25 seconds; control, 12 seconds). On July 11, a pericardial friction rub was heard for the first time and remained audible for the next three days. On July 25 the prothrombin percentage activity fell to 12% of normal levels. Inadvertently, the patient was given 100 mg. of bishydroxy-

coumarin on this day. On the following day prothrombin activity became further depressed, to a level of 6% of normal (patient's prothrombin time, 60 seconds; control, 12 seconds), and vitamin K was administered.

Several hours later the blood pressure fell to an average level of 100/60 mm. of Hg concomitant with a rising pulse rate. These signs of circulatory decompensation were associated with a recurrence of substernal pain. The patient became quite dyspneic and cyanotic, and manifested marked pallor. The neck veins became markedly distended and were pulsatile in the sitting position. Moist râles appeared over both lung fields posteriorly. The heart sounds were muffled. The liver edge was palpable 8 cm. below the right costal margin and was markedly tender.

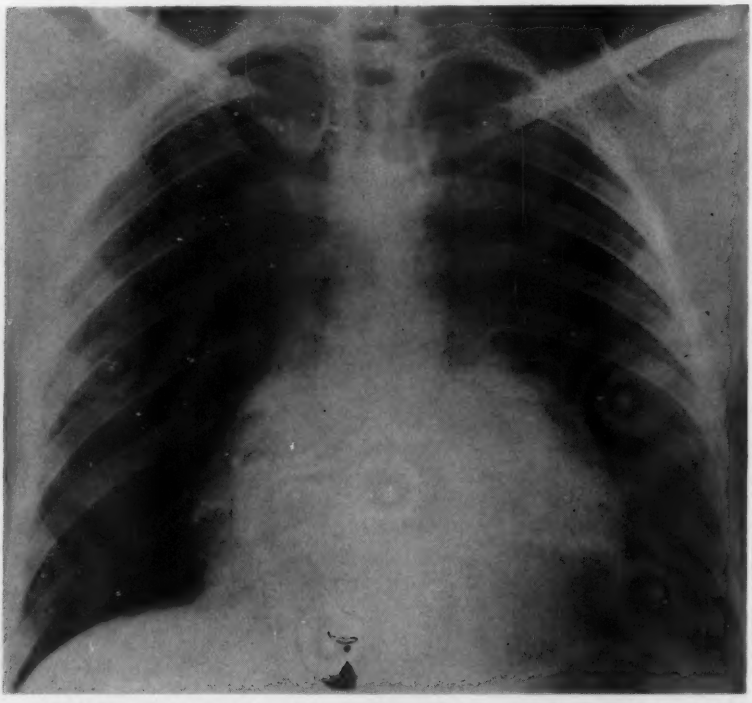


FIG. 3. Chest roentgenogram on July 27, 1954, showing pericardial effusion, with lungs and pleural spaces remaining essentially clear.

A roentgenogram of the chest (figure 3) showed a marked increase in cardiac size. The type of cardiac silhouette was consistent with pericardial effusion. Fluoroscopic examination showed minimal pulsations and considerable generalized enlargement of the cardiac silhouette. Hilar markings did not appear to be increased, and the upper mediastinum was not widened. An electrocardiogram showed no new evidence of myocardial injury. A hemogram revealed a white blood cell count of 7,200, with a normal differential and a hematocrit of 37%.

On July 27 pericardicentesis was performed via a subxiphoid approach, and 150 c.c. of dark, non-clotting, grossly bloody fluid were aspirated from the peri-

cardial sac. The fluid was negative for acid-fast bacilli on smear and culture. Following the procedure there was rapid clinical improvement. A roentgenogram of the chest showed diminution in the size of the cardiac silhouette. However, fluoroscopically the cardiac pulsations were still markedly diminished in amplitude. Because of the persistence of basilar moist râles the patient was digitalized. Through the month of August he remained dyspneic while lying in bed, although he did not complain of chest pain. The neck veins were distended in a sitting position, and there was minimal peripheral edema. Toward the latter part of the month, right lower chest pain heralded the appearance of right-sided pleural effusion. A thoracentesis yielded 1,700 c.c. of amber colored serous fluid. The specific gravity was 1.011, and the protein content was 2.5 gm.%. The fluid was negative for acid-fast bacilli on smear and culture.

During the months of September and October the patient's dyspnea at rest persisted and he developed two-pillow orthopnea. The blood pressure remained at a level of 100/80 mm. of Hg, and there was a persistent tachycardia of 100 to 110 per minute despite adequate digitalis maintenance dosage. Pulsus paradoxus was present. The classic findings of right-heart failure were present on physical examination. Serial chest roentgenograms showed that by October 1 the cardiac silhouette was similar in size to that noted on admission. The right pleural effusion persisted in spite of weekly thoracenteses. Each thoracentesis yielded 500 to 750 c.c. of fluid similar in nature to that obtained during the first aspiration. Repeated cultures of this fluid were negative for acid-fast bacilli; cell blocks and smears were negative for tumor cells. The Mantoux test was negative up to 1:100 dilution.

Antecubital venous pressure on October 15 was 28 cm. of water, with a rise to 42 cm. on right upper quadrant pressure. After 10 seconds of leg exercises the pressure rose to 45 cm., and returned to the initial level of 28 cm. after 30 seconds of rest. These determinations were representative of many recordings taken during the following four months. The circulation time (Decholin) was 15 seconds, and arm-to-lung (ether) time was 9 seconds on repeated determinations. White cell count, urinalysis, sedimentation rate and hematocrit were all within normal limits. The blood nonprotein nitrogen, total proteins and albumin/globulin ratio, sugar, cholesterol, calcium, phosphorus, sodium, potassium, chlorides and carbon dioxide content were normal. A needle biopsy of the liver showed moderate congestion confined to the central lobules; no evidence of fatty changes was noted. Phlebosclerosis was absent. Repeated cardiac fluoroscopic examinations showed diminution of the cardiac pulsation along the right and left borders. Careful study failed to reveal the presence of pericardial calcification. An electrocardiographic tracing representative of many taken during the last three months of 1954 showed low voltage in all leads, in addition to digitalis effect and myocardial ischemia (figure 2, October 2).

During November and December, 1954, and January, 1955, the patient was treated vigorously with digitalis, ammonium chloride, mercurials and low salt diet. On this regimen his peripheral edema subsided, and his weight returned to pre-admission levels, although dyspnea at rest and orthopnea persisted. On December 1 his vital capacity was 1.5 L. in 3 seconds. A representative chest roentgenogram taken during this period showed persistence of right pleural effusion (figure 4).

The clinical impression was that the patient had a constrictive pericarditis secondary to an organized hemopericardium. After his clinical condition had remained stable for several months an exploratory thoracotomy was performed on February 10, 1955, by Dr. S. Gwin Robbins, of Memphis. A transverse anterior incision was made through the right and left fourth intercostal spaces, thus exposing the heart, mediastinum and lower lobes of both lungs. The heart was compressed by a thickened, whitish pericardium which impaired cardiac mobility to such an

extent that scarcely any cardiac pulsation was noted. The pericardial sac itself was obliterated by this fibrous reaction. The constrictive process involved the inferior aspect of the superior vena cava; the inferior vena cava did not appear to be involved. No evidence of calcification was present. The collapsed lower lobe of the right lung was bound down by a mass of fibrinous pleural reaction and peel overlying the visceral pleura in this region.

Dissection and resection of the constricting scar, which measured approximately 1 cm. in thickness, were begun over the left ventricle; as the scar was removed the

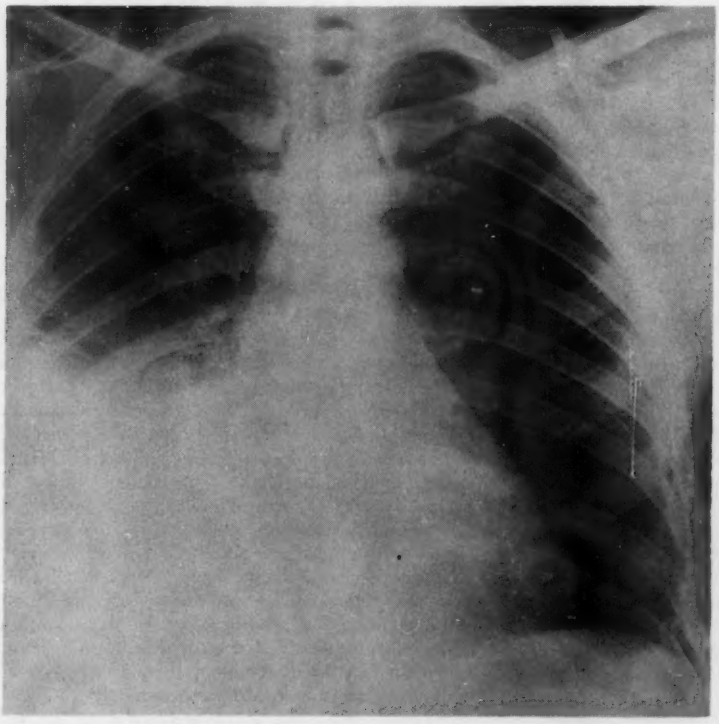


FIG. 4. This chest roentgenogram is representative of numerous films taken after September 1, 1954, showing marked right-sided pleural effusion. Size of cardiac silhouette is now similar to that seen on admission film.

imprisoned heart expanded markedly and normal cardiac pulsations were noted in the decorticated areas.

A portion of thinned-out myocardium was visualized on the lateral aspect of the left ventricle. The area was fibrotic and pale, and measured approximately 2 square cm. The constricting scar was attenuated and intimately adherent to this thinned-out area, which contracted weakly in systole. This was thought to represent a healed myocardial infarct, and this area was avoided in the dissection. The peel was stripped from the anterior and inferior surfaces of both ventricles, the anterior surface of the auricles and the superior vena cava. Posteriorly the decortication was

effected to an area 2 cm. posterior to the phrenic nerves, care being taken to avoid damage to these structures. The decortication of the lower lobe of the right lung was then performed, and complete expansion of the lower lobe was effected. Drainage was instituted in the right inferior pleural space and the chest wall was closed in layers. The patient withstood the operation well.

Microscopically, the sections of pericardium revealed granulation tissue and dense fibrous connective tissue containing a few small vessels with minimal perivascular lymphocytic infiltration. No cholesterol clefts were noted in any of the sections. Special stains for iron pigment revealed no hemosiderin. Fat stains demonstrated one focus of phagocytized lipid material near a small vessel. Acid-fast stains revealed no organisms.

One week following surgery the venous pressure was 24 cm. of water, and rose to 28 cm. with peripheral exercise. The neck veins were collapsed in a sitting position and only moderately distended in the horizontal position. The blood pressure persisted at about 110/70 mm. of Hg. Heart tones were good; the rate was 80 per minute. Digitalis was discontinued. Three weeks following surgery the venous pressure had dropped to 17 cm. of water. The vital capacity had increased to 2.5 L. in 3 seconds. A chest roentgenogram showed blunting of the right costophrenic sinus but was otherwise not remarkable. Cardiac fluoroscopy showed pulsations of normal amplitude along both heart borders. An electrocardiogram taken two months postoperatively (figure 2, April 10) showed an increase in the voltage in all leads. The patient, no longer dyspneic or orthopneic, had an uneventful postoperative course. He was discharged April 10, 1955, to be followed in the clinic.

Discussion and Comment

Anticoagulant therapy was instituted on admission because of the intractable pain and poor clinical condition. The course was uncomplicated until the nineteenth day of hospitalization, when the prothrombin activity became progressively depressed. Signs and symptoms of progressive bleeding into the pericardial sac soon followed, and culminated in tamponade. In recent years the occurrence of hemopericardium in association with the use of anticoagulant therapy for myocardial infarction has been well documented. It is of interest that while hemopericardium was developing in our patient, several clinical features were manifested which were similar to those noted in previously reported cases. Nichol,[5] Goldstein and Wolff[6] and Izzo and associates[7] all emphasized that recurrence of chest pain without renewed electrocardiographic evidence of recent myocardial injury was a noteworthy feature of developing hemopericardium. The cases presented by Izzo et al.[7] manifested unexplained anemia at the onset of hemopericardium, and the authors stressed this finding as a diagnostic aid. Similarly, in our patient the hematocrit, which was 46% on admission, dropped to a level of 37% coincident with the occurrence of cardiac tamponade, and persisted at that level during the following month.

Following pericardicentesis the patient's clinical condition rapidly improved. Although it was evident that only a fraction of the total amount of blood present in the pericardial sac had been removed, it was feared that repeated pericardicenteses might be hazardous because of the danger of puncturing necrotic myocardium with a needle. Moreover, the dramatic clinical response was a sufficient deterrent to further manipulation.

The onset of pleural effusion one month following the hemopericardium marked the beginning of a hospital course characterized mainly by signs and

symptoms of chronic cardiac compression. Although the major differential diagnosis was congestive heart failure, several important clinical phenomena negated this diagnosis. The circulation time was consistently within normal limits. Although the patient was adequately digitalized, tachycardia persisted. It was significant that the venous pressure was consistently elevated above 28 cm. of water, considerably out of proportion to the elevations usually seen in congestive heart failure. Even though the patient achieved adequate diuresis when treated with ammonium chloride, mercurials and digitalis, the venous pressure elevation persisted, again suggesting constrictive pericarditis.

In view of the mass of clinical evidence and supportive laboratory findings favoring a diagnosis of constrictive pericarditis, operation awaited the optimal physical and mental status of the patient. Operative findings were remarkable in that, in addition to the disclosure of an extensive constrictive pericarditis and pleuritis, a lateral wall infarction was visualized in vivo. The infarcted area demonstrated functional impairment, and its relation to the activity of the rest of the myocardium was clearly observed. On review of the electrocardiograms taken on admissions it is noteworthy that the tracings exhibited depressions of the S-T segments in V_{1-4}. In describing the electrocardiographic pattern of infarction of the lateral wall of the left ventricle, Wood, Wolferth and Bellet [8] mentioned depression of the S-T segment in Lead IV as a typical feature. Thomson and Feil [9] also noted S-T segment depressions in the chest leads in four autopsied cases of lateral wall infarction.

As was anticipated, histologic study of the resected pericardium indicated nonspecific chronic pericarditis and afforded no indication as to the etiology of the constriction. The sole clue was the finding of one focus of phagocytized lipid material on fat stain. This evidence, soon to be elaborated upon, favored hemopericardium as the antecedent of the constrictive process.

In 1929 while studying the effects of Dakin's solution injected into the pericardial sac of dogs for the treatment of purulent pericarditis, Beck [10] found that the injection of the solution into the normal pericardial sac resulted in immediate hemorrhage. This was followed in several weeks by pericarditis with effusion or generalized constrictive pericarditis. Daniel and Puder [11] in 1932 reported a case of cholesterol pericarditis wherein tuberculosis was invoked as an etiologic factor. At autopsy, cholesterol deposits were found in the pericardium. The authors suggested that tuberculous involvement of the pericardium may have resulted in hemopericardium, followed by the precipitation of cholesterol deposits and subsequent pericarditis. Paul White,[12] in the second edition of his textbook, mentioned that trauma resulting in hemopericardium may be a cause of constrictive pericarditis. Beck [13] in 1937 stated that "the heart can be compressed or partially strangulated through a traumatic rupture of parietal pericardium. The compression scar may be localized or generalized over the entire heart."

Cases of constrictive pericarditis following hemopericardium as a consequence of trauma to the anterior chest were recorded by Glenn,[14] Dejou,[15] Ada et al.,[16] Barker and Johnston,[17] McKusick [18] and Warburg.[19] Overholt and associates [20] reported the case of a patient who sustained a crushing chest injury and developed bilateral hematothorax and hemopericardium. This resulted in combined constrictive pericarditis and constrictive pleuritis over a five year period, which were corrected following pericardiectomy and bilateral pulmonary decortication. In a discussion of a paper by Elkin and Campbell [21] dealing with the treatment of car-

diac tamponade by aspiration, Maguire and Gage [22] both stated that blood clots formed readily in the pericardium. They suggested the possibility that blood clots left behind after aspiration become organized and lead to the development of constrictive pericarditis.

In 1952 Ehrenhaft and Taber [23] reported the case of a patient who developed hemopericardium following minimal trauma to the precordial area. At surgery an early constrictive pericarditis was found. These authors experimentally attempted to produce constrictive pericarditis in animals via intrapericardial injection of blood and blood lipids. A group of dogs received an intrapericardial injection of autogenous whole blood, and in a second group the lipid fraction of pooled dogs' blood was injected. The dogs were sacrificed at varying monthly intervals following injection. One animal in the lipid series demonstrated a well developed constrictive pericarditis. The remainder of the dogs in the lipid series showed lesser changes of constrictive pericarditis, while the animals of the whole-blood series showed the least change. These experimental findings were considered as evidence that, in some instances, constrictive pericarditis may be the outcome of pericardial hemorrhages. It would also appear that the lipid fraction of blood was probably the significant component in the production of the inflammatory pericardial reaction. In the animal who showed the well developed changes of constrictive pericarditis, fat stains demonstrated phagocytized lipid material within the scarred epicardium and pericardium. It is interesting to note that fat stains of the pericardium resected from our patient demonstrated one focus of phagocytized lipid material near a small blood vessel.

This report represents the first case in the literature wherein hemopericardium following bishydroxycoumarin intoxication in all probability resulted in the development of constrictive pericarditis. To avert the possible formation of constrictive pericarditis in cases of hemopericardium, it would appear that complete evacuation of the blood from the pericardial sac is mandatory. It is interesting that in the experiments performed by Ehrenhaft and Taber [23] as little as 100 c.c. of blood injected into the pericardial sac of the dogs was sufficient to cause changes of constrictive pericarditis. It may reasonably be concluded that in cases where repeated pericardicenteses are contraindicated, as was the situation in our case, pericardiotomy with visual exploration and thorough drainage would be the procedure of choice.

It may also be inferred that careful attention must be given those cardiac patients with histories of having previously been on anticoagulant therapy for myocardial infarction. It is possible that hemopericardium may have resulted from the seepage of small amounts of blood into the pericardial sac at the time of anticoagulant administration. Signs and symptoms of cardiac compression later in the clinical course might then represent the development of constrictive pericarditis. Realization by the clinician of the possibility of occurrence of this sequence of events would then be of major import in the subsequent management of the patient.

Summary

1. A case is presented of a patient who developed constrictive pericarditis several months following hemopericardium. The hemopericardium probably resulted from bishydroxycoumarin toxicity.

2. This report adds further clinical evidence that there is an etiologic association between hemopericardium and the subsequent development of constrictive

pericarditis. A review of the literature reveals several cases of traumatic and experimental hemopericardium that manifested this sequence of events.

3. The occurrence of hemopericardium as a possible complication resulting from the use of anticoagulants in myocardial infarction is reëmphasized.

Acknowledgment

I am indebted to Dr. Tracy Levy, Chief of the Medical Services at the U. S. Public Health Service Hospital, Memphis, Tennessee, for his assistance and suggestions in the preparation of this manuscript. I also wish to thank Dr. L. Castleman and Dr. I. Kroop for their helpful criticisms. The Medical Illustration Laboratory of the V. A. Medical Teaching Group Hospital of Memphis prepared the illustrations.

Summario in Interlingua

In multe casos de pericarditis constrictive, le examine histologic del resectionate pericardio non revela le precise agente etiologic que es responsabile pro le processo constrictive. Le caso hic presentate exhibi aspectos clinic que reinfortia le concepto del importantia etiologic de hematopericardio in le disveloppamento de pericarditis constrictive.

Es describite le curso clinic in le caso de un masculo blanc de 41 annos de etate qui disveloppava hematopericardio como complication del tractamento anticoagulatori de un infarcimento myocardial. Le tamponage hemorrhagic del pericardio esseva alleviate in parte post pericardiocentese. Le menses sequente videva le disveloppamento del signos e symptomas typic de pericarditis constrictive. Un exploration chirurgic confirmava le presentia del constriction, e pericardiectomia resultava in un frappante melioration clinic.

In le discussion le autor sublinea le signification del occurrentia de hematopericardio como un complication possibile de therapia anticoagulatori in infarcimento myocardial. Le recurrentia de dolores thoracic sin nove signos electrocardiographic de un recente lesion myocardial e le disveloppamento de un non-explicabile anemia es mentionate como importante phenomenos clinic prognosticante le declaration de hematopericardio. Le aspectos del diagnose differential de pericarditis constrictive es discutite brevemente. Es presentate un detaliate revista del litteratura in re hematopericardio como precursor de pericarditis constrictive. In le majoritate del casos reportate, pericarditis constrictive se disveloppava como sequela de hematopericardio traumatic. Le production experimental de hemorrhagia intrapericardial esseva etiam sequite per le disveloppamento de pericarditis constrictive. Le autor signala le constatation histologic de phagocytisate materiales lipidic intra le pericardio cicatrisate in un del casos experimental citate. Ille nota que in le caso hic presentate, un simile phenomeno esseva manifeste.

Es formulate le conclusion que in casos ubi repetite pericardiocenteses es considerate como riscose, le methodo de election es probabilemente pericardiotomia con exploration visual e drainage del sacco pericardial.

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SERUM LIPIDS IN LIPEMIA RETINALIS: REPORT OF A CASE *

By Edward C. Franklin, M.D., *New York, N. Y.*, and
Milton Weissman, B.S., *Bronx, N. Y.*

Lipemia retinalis and xanthoma diabeticorum are occasionally seen in patients with diabetes mellitus and are thought to be due to abnormalities in the serum lipid fractions. Since the first description of lipemia retinalis by Heyl in

* Received for publication September 28, 1955.
From the Department of Medicine, and Laboratory Service, Veterans Administration Hospital, Bronx, N. Y.
Requests for reprints should be addressed to Edward C. Franklin, M.D., The Rockefeller Institute for Medical Research, Sixty-sixth Street and York Avenue, New York 21, N. Y.

1880,[1] only about 68 cases have been reported in patients with diabetes. To the best of our knowledge only seven of these have had complete determinations of the lipid fractions at the time of diagnosis, and only five of these were studied after the disappearance of the eye findings.[2, 3, 4] Experimental procedures designed to elucidate the pathogenesis of lipemia retinalis are difficult to carry out because of the relative rarity and the transitory nature of the changes. The following case, the eighth with complete determinations of lipid fractions, is there-



FIG. 1. Xanthomata on buttocks and extensor surfaces of arm and forearm six days after admission.

fore presented in an effort to evaluate factors contributing to the characteristic retinal changes in lipemia retinalis.

CASE REPORT

History: A 37 year old Negro male was admitted to the hospital because of dizziness of two weeks' duration. One month prior to admission the patient had developed polyuria, polydipsia and a 20 pound weight loss in spite of a normal appetite. Two weeks later he became dizzy and fatigued, and five days prior to admission he noted the appearance of painless lumps on his buttocks. In 1952 the patient had been told that he had mild essential hypertension. One brother, aged 43, had diabetes. The parents and eight other siblings did not have diabetes.

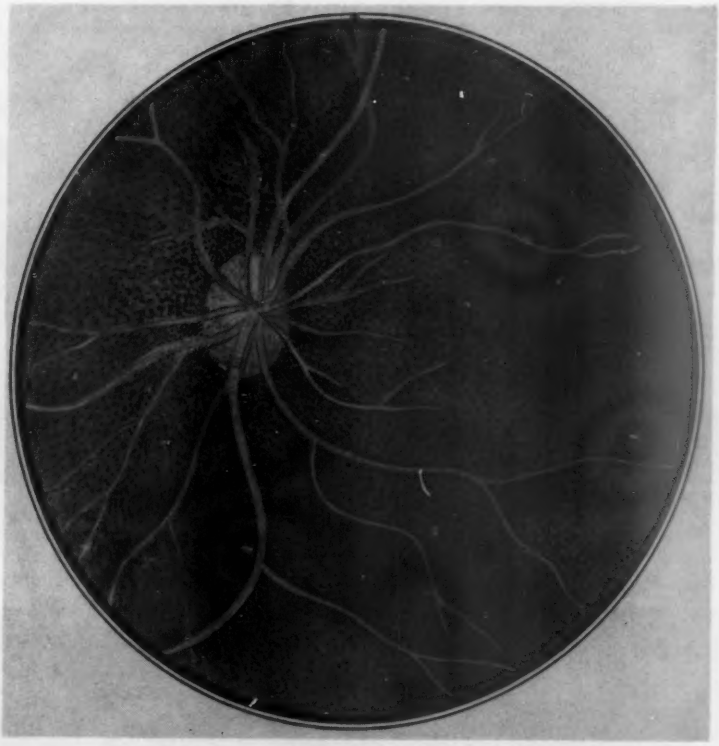


FIG. 2. Drawing of fundus, showing lipemia retinalis one day after admission.

Physical Examination: On admission the patient was a well developed, well nourished, alert Negro male in no distress. The temperature was 98° F.; pulse, 86 per minute; blood pressure, 150/100 mm. Hg; respirations, 20 per minute; weight, 175 pounds. Physical examination was entirely normal except for the presence of

TABLE 1

Serum Lipids in a Case of Lipemia Retinalis

Day	Total Fat (mg.%)	Cholesterol Total (mg.%)	Cholesterol Esters (mg.%)	Phospholipids (mg.%)	Neutral† Fat (mg.%)	Phospholipid Total Fat Ratio	Degree of Lipemia	
							Fundi	Serum
1	12,480	926	394	2,387	9,167	0.19	4+	4+
2	10,800	926	394	1,187	8,687	0.11	4+	4+
3	8,600	900*	—	900	6,800	0.10	2+	3+
6	4,250	750*	—	630	2,870	0.15	0	2+
11	—	615	437	—	—	—	0	1+
23	1,750	445	320	463	842	0.27	0	0
27	—	436	347	—	—	—	0	0
47	810	254	170	320	236	0.40	0	0

* Estimated.

† Calculated: Neutral Fat = Total Fat − (Total Cholesterol + Phospholipid).



FIG. 3. Sera drawn during hospital stay, showing decreasing lactescence and eventual clearing.



FIG. 4. Pigmented areas on buttocks and extensor surfaces of arms and forearms six weeks after admission.

many 1 to 3 mm. discrete, elevated yellowish papules scattered over both buttocks and the extensor surfaces of the arms and forearms (figure 1). The fundi were pale and the discs were sharp. There were no hemorrhages or exudates. The retinal vessels throughout their course were pinkish yellow in color and flat. There was no arteriolar light reflex, and arterioles and veins could be distinguished only by their size (figure 2).

Laboratory Studies and Course in Hospital: On admission, urinary sugar and acetone were 4 plus. The initial blood specimen appeared cloudy and had a purplish tint. On standing it separated into a normal layer of cells and a reddish white, opaque, creamlike supernatant which solidified on standing at room temperature. The blood sugar on admission was 329 mg.%, and the CO_2 combining power was 8.1 mEq./L. The patient was placed on a 2,545 calorie diabetic diet and received 190 units of regular insulin during the night. The next morning his urines were negative for glucose and acetone. His blood sugar was 94 mg.%; CO_2 combining power, 20.3 mEq./L. Serum electrolytes, electrocardiogram and x-ray examination of the chest were normal. The total protein was 6.5 gm.%; serum albumin, 3.3 gm.%; serum globulin, 3.2 gm.%. The thymol turbidity test was 97.6 units. He was started on NPH insulin and his diabetes was easily controlled, requiring 30 units of NPH insulin a day at the time of discharge. Serum lipid studies during his hospital course are listed in table 1. The retinal vessels continued to appear very lipemic for two days, and gradually returned to normal by the sixth day. The serum became progressively less lipemic and was clear in 17 days (figure 3). The skin lesions, shown to be xanthomata by biopsy, gradually faded and flattened. At the end of one month only darkly pigmented areas remained, and at the end of two months the lesions had entirely disappeared (figure 4).

Discussion

Lipemia retinalis is a rare manifestation of a disturbance in serum lipids, most commonly associated with diabetes. Since the original description by Heyl [1] in 1880, about 68 cases have been reported in diabetic patients, and a smaller number in nondiabetics. Retinal lipemia is seen in both sexes and in every age group, most commonly in the second and third decades. When diabetes is present it is almost always complicated by acidosis. The appearance of the fundi is striking and pathognomonic. The vessels are flat and ribbon-like. They are pale yellow or salmon pink in color. The arteriolar light reflex becomes diffuse or disappears, thus making differentiation of arterioles and veins dependent upon their size alone. The disc and fundus usually appear normal, although the fundus may be pale if the choroidal vessels are involved. The changes are transient, appear first and persist longest at the periphery, and disappear as the diabetes is controlled, sometimes within 48 hours. Usually there is no visual disturbance.[2]

The serum of patients with lipemia retinalis is grossly milky or "lipemic." This turbidity is thought to account for the characteristic appearance of the retinal vessels. Lipemia retinalis is never seen in the absence of hyperlipemia, but hyperlipemia alone does not produce a milky serum or the retinal picture. The observed changes are probably due to an abnormality in the proportion of the lipid fractions. Serum lipids are composed of four fractions: free cholesterol, cholesterol esters, phospholipids and neutral fats. Serum appears clear because these substances exist as colloidal particles with diameters of less than 0.1 μ while larger particles make the serum turbid.[5]

Boyd [6] in 1937 found that lipemic sera contained a higher proportion of neutral fats than did clear sera, and pointed out the importance of phospholipids in maintaining the clarity of serum. He suggested that turbidity might be due to a relative insufficiency of phospholipids. In 1949 Ahrens and Kunkel [5] confirmed this theory. In a study of hyperlipemic sera, some clear and some turbid, they noted that a major component of the clear sera was phospholipids, while in nephrotic lipemic sera neutral fat predominated. They attributed the solubilizing effect of phospholipids on the hydrophobic lipid fractions to their strong surface action, thus preventing their coalescence to visible sized particles. In a later report Ahrens [7] stated that, in lipemic sera, phospholipids made up less than 29% of total lipids by weight, while in clear sera the proportion was over 30%. More recently, Albrink, Man and Peters [8] have stated that the only change necessary for the appearance of lactescence is an elevation of neutral fat. The patient presented in this report had a marked elevation of all the serum lipids, especially the neutral fat fraction, at the time of admission. The phospholipid level was also elevated, but was proportionally less than the rest of the serum lipids. As the diabetes was brought under control the lipemia retinalis disappeared, at a time when the serum was still grossly lactescent and the serum lipids were markedly elevated. This again confirms the observation that lipid levels may be quite high before lipemia retinalis becomes evident. Analysis of lipid fraction studies of all the carefully studied cases of lipemia retinalis reported to date shows that all eight had an initial elevation of neutral fat, and a phospholipid total lipid ratio of less than 0.30. The neutral fat approached normal values in each of five cases studied after recovery, while the phospholipid total lipid ratio was greater than 0.30 in four of the five. A sixth case was studied for three days only and the results are therefore inconclusive.

Studies of lipoproteins by means of the ultracentrifuge in diabetic acidosis have recently been described by Gofman and his associates [9] and by Tuller and coworkers.[10] One of the patients in the latter report presented with lipemia retinalis. At the time of admission there was a marked elevation of the low density lipoproteins of the S_f 21–100 class. With treatment there was gradual reversion toward normal, with a transient rise and subsequent fall in the S_f 12–20 group of lipoproteins. No ultracentrifugal studies were carried out on the serum of the patient here reported, and the exact rôle of these changes in the lipemia retinalis cannot be evaluated. Obviously the number of cases is too small to determine the exact cause of lactescence of hyperlipemic sera seen in lipemia retinalis, and careful lipid fraction studies utilizing all methods available are indicated in similar cases seen in the future.

Summary

1. A case of lipemia retinalis is reported.

2. Serum lipid studies during the course of the patient's illness are presented and correlated with the clinical findings and the appearance of the serum.

3. The possible causes of lactescence of hyperlipemic sera are discussed, and an attempt is made to determine whether they are applicable in lipemia retinalis.

4. It is suggested that careful lipid fraction studies be undertaken in all such cases in the future.

Summario in Interlingua

Lipemia retinal es un manifestation rar de un disturbation de lipidos seral e se trova associate le plus communmente con diabete mellite. Illo occurre in ambe sexos e a omne etates, le plus frequentemente durante le secunde e le tertie decennio del vita. Le diabete es usualmente accompaniate de acidosis. Le apparition del fundos es pathognomonic. Le vasos es platte e de color jalne o rosa salmon, e le arteriolas e venas es distinguibile solmente per lor dimensiones. Iste constatationes es transiente e dispare quando le diabete es regulate. Circa 68 casos ha essite reportate in patientes diabetic. Solmente septe de illes ha habite complete determinationes del fractiones del lipidos seral.

Es presentate le caso de un negro mascule de 37 annos de etate, con symptomas de diabete de quatro septimanas de duration e constatationes de lipemia retinal, xanthoma de diabeticos, e leve grados de acidosis. Le diabete esseva facilemente regulate per medio de insulina e prescriptiones dietari. Le lipemia retinal comenciava meliorar se intra duo dies, e le fundos esseva normal post sex dies. Le sero esseva grossiermente lipemic al tempore del admission al hospital e se clarificava gradualmente in le curso de 17 dies. Le xanthomas dispareva intra duo menses. Le valores del lipidos seral es monstrate in forma tabular.

Le sero de patientes con lipemia retinal es de apparentia lactose o "lipemic." Iste turbiditate explica le apparition del vasos retinal. Le lactositate del sero non resulta exclusivemente de hyperlipemia sed es probabilemente causate per un anormal distribution del quatro major fractiones lipidic, Isto es possibilemente le effecto de un simple augmento de grassia neutre, sed illo representa plus probabilemente un insufficientia relative del phospholipidos. Le patiente del presente reporto e etiam le majoritate del patientes discutite in previe reportos exhibiva ambe le mentionate anormalitates. Pro determinar le exacte causa del lactositate de seros hyperlipemic, studios meticulose del lipidos seral es necessari in omne simile casos incontrate in le futuro.

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HOMOZYGOUS HEMOGLOBIN C DISEASE IN A 79 YEAR OLD MAN WITH GOUT*

By James W. Ransone, Captain, MC, and Robert D. Lange, Captain, MC,
Washington, D. C.

Though a new form of hemoglobin, hemoglobin C, was reported in 1950 and 1951,[1, 2] it was not until 1953 that homozygous hemoglobin C disease was described.[3, 4] Since that time the disease has been found repeatedly, but usually in the younger age groups. We wish to report what we believe to be the oldest living person with homozygous hemoglobin C disease—a 79 year old Negro man. Interestingly enough, he also had gout, a condition infrequently reported in the Negro race.

Case Report

A 79 year old male Negro was admitted to Walter Reed Army Hospital in November, 1954, with the chief complaint of 10 days of fever and burning on urination. Past history revealed that anemia of approximately 8 to 10 gm. had been discovered elsewhere in 1950 and diagnosed as pernicious anemia. Treatment consisted of oral and parenteral vitamin B_{12} and liver extract, but there was no improvement on this medication. There was no history of jaundice, but for many years the patient had had intermittent episodes of severe joint pain involving knees, ankles and feet, with occasional swelling. This pain subsided after a period of days to weeks, but a definite diagnosis was never made.

Physical examination revealed a senile, emaciated Negro with extreme pallor of his mucous membranes. The spleen was felt 4 cm. below the left costal margin and was quite firm and smooth. Several subcutaneous tophi were scattered over the dorsa of the feet. There was a bilateral knee effusion of moderate degree. Neurologic examination was consistent with mild paralysis agitans.

Laboratory Data: Hemoglobin, 6.5 gm.%; hematocrit, 19%; red blood count, 2.7 million per cubic millimeter; mean corpuscular volume, 78 cubic microns; mean corpuscular hemoglobin, 25 micromicrograms; mean corpuscular hemoglobin concentration, 32%; reticulocyte count, 2.1%. Blood smear showed severe anisocytosis, poikilocytosis, a few target cells, 2 nucleated red blood cells per 100 white blood cells and folded red blood cells (figure 1). White blood count, 31,000, with 94% neutrophils (8 stabs) and 6 lymphocytes; platelets, 490,000. Bone marrow examination showed a myeloid-erythroid ratio of 1.5 to 1 and was otherwise normal. Sickling of the red blood cells was negative with sodium bisulfite. There was increased mechanical fragility with decreased osmotic fragility with 36% hemolysis of incubated red blood cells at 0.46% sodium chloride, as opposed to 84% hemolysis of incubated control red blood cells. Erythrocyte survival studies with radioactive chromium ^{51} tagged red blood cells of the patient demonstrated 50% survival after 19 days, with a control of 50% survival after 30 days (figure 2). Paper electrophoresis by the Akeroyd modification of the Durrum-Motulsky method[5] demonstrated only the slow component compatible with hemoglobin C (figure 3). Total

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From the General Medicine Service No. 3 and the Hematology Service, Walter Reed Army Hospital, Walter Reed Army Medical Center, Washington, D. C.
Requests for reprints should be addressed to Captain James W. Ransone, MC, Walter Reed Army Hospital, Walter Reed Army Medical Center, Washington 12, D. C.

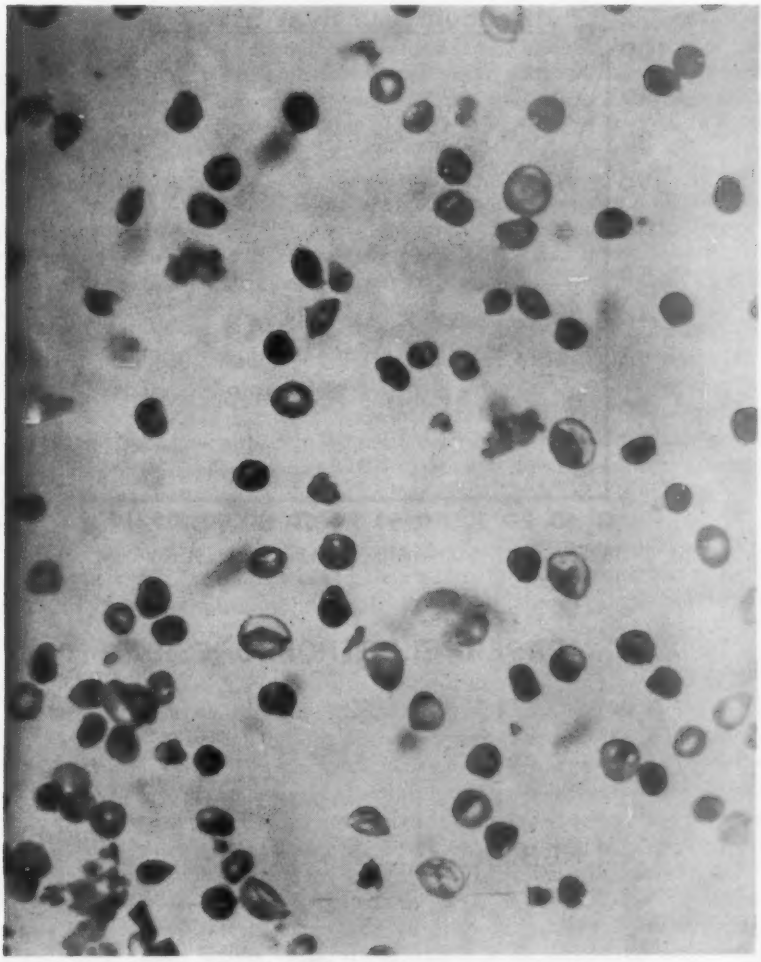


FIG. 1. Photomicrograph of patient's blood smear demonstrating folding of the red blood cells.

serum bilirubin was 2.3 mg.%, with a direct of 0.5 mg.%. Fasting blood uric acid was 11.8 and 10.1 mg.% on two occasions. Blood urea nitrogen was 32 mg.% and later fell to normal. Urinalysis revealed many white blood cells per high power field, and culture grew *Aerobacter aerogenes* and *Streptococcus faecalis*. Free hydrochloric acid was present on gastric analysis after histamine had been given. X-rays of the feet showed several punched-out, osseous lesions compatible with gout. On cholecystography, multiple-faceted radiopaque stones were seen, and there was poor concentration of contrast material in the gall-bladder. Twelve days after admission the white blood count fell to 7,500, with normal differential.

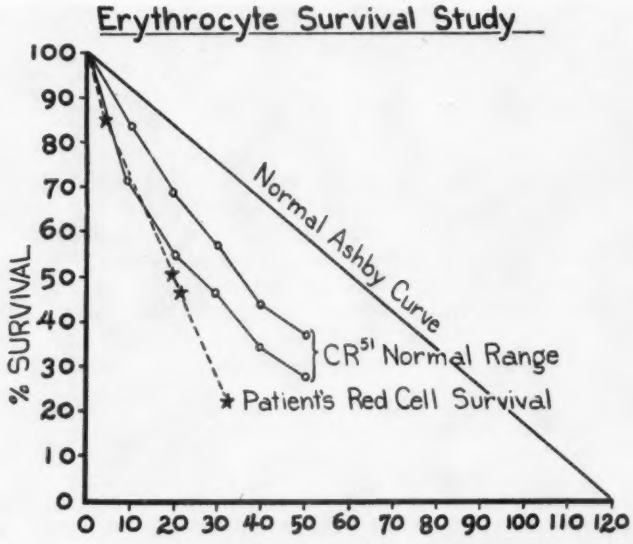


FIG. 2. Patient's red cell survival by chromium 51 tagged red blood cells.

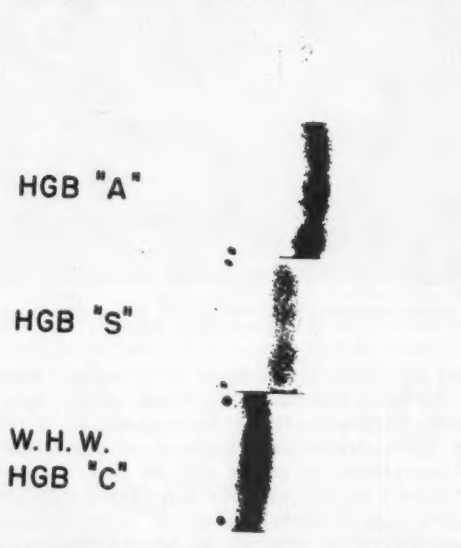


FIG. 3. Electrophoretic pattern demonstrating slow component of hemoglobin C as opposed to normal hemoglobin A and sickle cell hemoglobin S.

Discussion

This man had a severe anemia, an elevated serum bilirubin, and a bone marrow showing erythroid hyperplasia. Paper electrophoresis, as previously described, demonstrated homozygous hemoglobin C disease. Following several packed red cell transfusions, his hemoglobin rose to 10 gm., but during eight months of observation it ranged between 8 to 10 gm. His gout was treated initially with colchicine, and later with Benemid, with his blood uric acid falling to approximately 5 mg.%. This patient had a definite hemolytic anemia complicated by a urinary tract infection. However, the low value of the reticulocytes and the lack of a more marked erythroid hyperplasia in the bone marrow bring up the possibility that he was seen at the end of an aregenerative crisis. The white blood cells and platelets apparently were not affected. His urinary tract infection finally cleared on Aureomycin.

Ranney et al.[5] described one of the first cases of homozygous hemoglobin C disease in 1953 in a 35 year old Negro woman, and Spaet [4] in 1953 reported the case of a four year old Negro boy. Most of the reported patients have been under 50 years of age, although Ranney [6] described a case of the homozygous form in a 52 year old Negro man. The disease is not one of severe hemolytic crisis, and apparently longevity is not affected. It is a familial disease which occurs almost exclusively in the Negro race.

The association of gout with hemolytic anemias is well known,[7] and though gout is not commonly reported in the Negro race, this case conformed to all the diagnostic features—podagra, hyperuricemia, subcutaneous tophi and osseous tophi.

This patient had never had any children, and his contemporary relatives were dead, so that a study of his family was impossible.

Intracellular crystals of hemoglobin, as reported by Diggs et al.,[8] were not found in this patient's blood, but the phenomenon of folding of the red blood cells was present. Features of homozygous hemoglobin C disease are: (1) chronic mild anemia; (2) splenomegaly; (3) many target cells in the peripheral blood smear; (4) bone marrow showing erythroid hyperplasia; (5) increased resistance of red blood cells to hypotonic saline solutions, and (6) evidence of increased red blood cell destruction manifested by elevated indirect serum bilirubin, elevation of reticulocyte count, and shortened red cell survival. At present the only definite means of diagnosis is the characteristic electrophoretic pattern. The apparently benign nature of this familial hemolytic anemia is evidenced by the longevity of this patient.

Summary

We have presented a case of homozygous hemoglobin C disease with associated gout in a 79 year old Negro man, and to our knowledge, he is the oldest living individual with this hemolytic anemia.

Acknowledgments

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SUMMARIO IN INTERLINGUA

"Morbo a hemoglobina C homozygotic" esseva primo discoperite in 1953. Secundo nostre informationes, le etate de omne patientes usque nunc reportate esseva infra 50 annos e in le majoritate del casos infra 30 annos. Le hic reportate caso concerne un patiente mascule negre qui habeva 79 annos de etate quando su anemia hemolytic esseva primo notate. Ben que gutta es supponitemente rar in negros, le patiente habeva le aspectos classic de gutta, con podagra, hyperuricemia, e tophos subcutanee e ossee. Tamen, le association de anemia hemolytic con gutta non es rar. Ben que le patiente esseva tractate initialmente per transfusion sanguinee, su anemia ha requirite nulle therapia additional e ille mantene un nivello de hemoglobina de inter 8 e 10 g. Morbo a hemoglobina C homozygotic es apparentemente libere de sever crises hemolytic. Le longevitate del patientes non pare esser afficite per illo. Le morbo es familial e occurre exclusivemente in le racia negre. Aspectos characteristic de morbo a hemoglobina C homozygotic es (1) leve anemia chronic, (2) splenomegalia, (3) numerose cellulas a oculo de ave in le frottis peripheric, (4) hyperplasia erythroide in le medulla ossee, (5) augmento del resistentia de erythrocytos a hypotonic solutiones salin, e (6) signos de augmento del destruction de erythrocytos, manifeste in elevate valores del indirecte bilirubina seral, in elevate numerationes del reticulocytos, e in un reducite superviventia del cellulas rubie. Al tempore presente il existe solmente un medio definitive pro le diagnose. Isto es le characteristic conformation electrophoretic.

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EDITORIAL

SEROTONIN

THE intestinal tract has long been considered the source of powerful chemical agents. This philosophy was formalized by Metchnikoff, and gave rise to the theory of autointoxication prevalent in the early decades of the twentieth century. Within the last few years workers in many fields in many countries have seen their researches converge upon a potent substance which might well be one of the powerful amines envisioned by Metchnikoff.

For the last 100 years it has been known to physiologists that the vasoconstrictor properties of the blood increase when blood clots. This constituted a serious problem for the investigators who tried to develop organ perfusion methods using blood. Several different solutions were found to the vasoconstrictor problem, which was encountered also in unclotted blood when it was subjected to the mechanical trauma of perfusion pumps. Incidently, this might be considered in contemporaneous use of "artificial heart" machines for cardiac surgery. The most successful technics were the use of the heart-lung preparation, and the inclusion of a surviving liver in the perfusion system.

Both of these methods caused the loss of the vasoconstrictor principle of the blood, and it is now known that lung and liver are particularly rich in the enzyme that destroys this substance.[1]

Rapport, Green and Page [2, 3] isolated this vasoconstrictor substance from beef serum and identified it as 5-hydroxytryptamine, a compound closely allied in structure to indican, long known to be present in excess in the urine in various debilitating conditions. Corcoran coined the term "serotonin" for this active principle.[4] Rand and Reid [5] in Australia found that the serotonin of blood was actually present only in the platelets, and that it was released from the platelets on clotting.

Erspamer, in Italy, studied a vasoconstrictor principle found in the gastrointestinal tract.[6, 7] In a classic series of researches, he described its properties, gave it the name "enteramine," and found it to be the most potent

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component of venom of the toad.[8, 9] It may be of more than passing significance that in this venom there is found another amine, adrenalin, and that there is no other example in nature of a hormone being found in external secretions. Erspamer considered enteramine to be the hormone of the enterochromaffin system.

The Italian investigator identified enteramine as 5-hydroxytryptamine,[9, 10] and it was now clear that the vasoconstrictor principle of the blood was present in very high concentrations in the enterochromaffin system.

Lembeck found that carcinoid tumors, called argentaffinomas because of their characteristic staining with silver, contained very large amounts of serotonin.[11] Shortly afterward a Scandinavian group, including the chemist Waldenström, whose classic researches in porphyrin metabolism are well known, described a bizarre syndrome seen in patients with metastatic malignant carcinoid. The clinical picture included cyanotic flushing, marked fluctuations of blood pressure, diarrhea and asthma. At autopsy, right-sided endocardial fibrosis and valvulitis with bronchoconstriction were found.[12] They speculated that these symptoms might be caused by serotonin liberated by the tumor on the basis of Lembeck's work, and were able a few months later to show that all of the clinical symptoms could be reproduced by the administration of serotonin, and that there was a large amount of serotonin in the blood of patients with the syndrome of malignant carcinoid.[13] This was confirmed shortly afterward in a joint communication from Page's and Udenfriend's groups.[14]

At the National Institutes of Health, Brodie's group had been studying the mechanism of action of drugs active on the central nervous system, and Udenfriend had been investigating the metabolism of aromatic amino acids. The highly productive collaboration between Udenfriend, who handled the chemical investigations, and Sjoerdsma, who furnished the clinical direction, is an outstanding example of the potentialities inherent in this research organization. Udenfriend developed specific and sensitive methods [15] for the measurement of serotonin in blood, opening up the field to a more de-

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tailed study of the metabolism of this compound. They also developed a quantitative test for 5-hydroxyindoleacetic acid [16, 17] in urine. The appearance of these two methods stimulated many clinical groups to undertake the search for and study of carcinoid tumors.

Further work by the Udenfriend group quickly established the fact that 5-hydroxyindole compounds were derived from the amino acid tryptophane, and a number of steps in the process were elucidated.[18] It is apparent now that the first step is the addition of a hydroxyl group to the 5 position of tryptophane to form a new amino acid, 5-hydroxytryptophane. This step probably occurs only in the liver. This compound has been shown to stimulate the formation of serotonin in animal brain,[19] and to cause many of the symptoms of the carcinoid syndrome in human beings.[20] The second step is the loss of carbon dioxide from the amino acid to form serotonin. This reaction occurs in the wall of the gut, the liver, the kidney and presumably the brain,[21] and accounts for the formation of serotonin in these organs.

The inactivation or further metabolism of serotonin occurs by the action of an enzyme found in most tissues—amine oxidase. This enzyme converts serotonin to an acid by oxidation of the amine group. In this process, all of its physiologic activity is lost and the excretory product, 5-hydroxyindoleacetic acid, is formed. In malignant carcinoid the urinary excretion of this metabolite is increased markedly, and this provides an easy method for the detection of such tumors.[17] No conditions have been detected in which the excretion of this substance is enhanced, other than malignant carcinoid.[22] If metastases of the tumor remain after the primary growth has been removed, the excretion of 5-hydroxyindoleacetic acid remains high, but if the tumor is removed completely the excretion of this acid is normal.[23, 20]

The physiologic significance of serotonin is implied by its potency in the central nervous system, the gastrointestinal tract, the cardiovascular system and the blood. It deserves the rôle of hormone first ascribed to it by Erspamer.

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[23] Borges, F., and Bessman, S. P.: Urinary excretion of 5-hydroxyindoleacetic acid. A. Serotonin metabolite, in hypertensive renal vascular disease, Proc. Soc. Exper. Biol. and Med., in press.

The finding by Stoll [24] that a serotonin analogue provoked schizophrenia-like symptoms, together with evidence of central nervous system activity of serotonin analogues,[25] led Wooley [26, 27] to propose that interference with serotonin metabolism in brain might be the cause of certain types of mental disease. The demonstration of serotonin in brain by Gaddum's group [28] lent support to this thesis. It was difficult, however, to cause central nervous system symptoms by the use of parenteral serotonin, although most of the peripheral symptomatology of malignant carcinoid could be reproduced.[29] This has led to the assumption that there must be a specific decarboxylase for 5-hydroxytryptophane in brain, and thus that the brain makes its own serotonin from the precursor formed in the liver. Support for this view comes from the finding by Udenfriend's group [19] that the administration of 5-hydroxytryptophane to experimental animals leads to great increases in the serotonin content of the brain.

Brodie's extensive studies of the pharmacology of drugs active in the central nervous system resulted in his discovery that reserpine causes a discharge of serotonin from brain,[30, 31] intestines,[32] and platelet,[21] and results in the urinary excretion of large amounts of 5-hydroxyindoleacetic acid, the end-product of serotonin metabolism. This finding led to the hypothesis developed by Brodie that serotonin in brain exists in an inactive, bound form. The serotonin is released by certain substances such as reserpine. While the serotonin is bound it is physiologically inert, and also is not subject to destruction by the amine oxidase normally present in brain. When it is released it exerts its pharmacologic effect and is also inactivated. The toxic effect of Marsalid, an inhibitor of amine oxidase, can be ascribed to its prolongation of the action of serotonin by preventing the destruction of the amine.[32]

The effect of chlorpromazine on the isolated gut indicates that it acts by blocking the sites at which serotonin is active.[33] This explanation of the

[24] Stoll, W. A.: Lysergsäure—Diaethylamid, ein Phantastikum aus der Mutterkorngroppe, Schweiz. Arch. f. Neurol. u. Psychiat. **60**: 279, 1947.

[25] Wooley, D. W., and Shaw, E.: An antiserotonin which is active when fed, J. Pharmacol. and Exper. Therap. **108**: 87, 1953.

[26] Wooley, D. W., and Shaw, E.: A biochemical and pharmacological suggestion about certain mental disorders, Proc. Nat. Acad. Sc. **40**: 228, 1954.

[27] Wooley, D. W., and Shaw, E.: Some neurophysiological aspects of Serotonin, Brit. M. J. **2**: 122, 1954.

[28] Amin, A. H., Crawford, T. B. B., and Gaddum, J. H.: Distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog, J. Physiol. **126**: 596, 1954.

[29] Waldenstrom, J., and Ljungberg, E.: Studies on the functional circulatory influence from metastasizing carcinoid tumours and their possible relation to enteramine production, Acta med. Scandinav. **152**: 311, 1955.

[30] Brodie, B. B., Pletscher, A., and Shore, P. A.: Evidence that serotonine has a role in brain function, Science **122**: 918, 1955.

[31] Brodie, B. B., Pletscher, A., and Shore, P. A.: Interaction of reserpine, serotonin, and lysergic acid diethylamide in brain, Science **122**: 374, 1955.

[32] Sjoerdsma, A., Smith, T. E., Stevenson, T. D., and Udenfriend, S.: Metabolism of 5-hydroxytryptamine by monoamine oxidase, Proc. Soc. Exper. Biol. and Med. **89**: 36, 1955.

[33] Benditt, E. P., and Rowley, D. A.: Antagonism of 5-hydroxytryptamine by chlorpromazine, Science **123**: 24, 1956.

action of chlorpromazine does not account for a recent observation that chlorpromazine diminished the excretion of 5-hydroxyindole acetic acid in a patient with carcinoid.[34] Marrazzi's report [35] that serotonin acts by blocking synaptic transmission needs further neurophysiologic data to put it into proper perspective.

The cardiovascular phenomena associated with serotonin excess have been reviewed by Waldenström.[36] The primary symptoms are intermittent flushing of the skin and tachycardia. The patient has cyanosis with peculiar vasodilatation. Frequently there are signs of pulmonary stenosis with right heart failure, and the hepatomegaly of passive congestion. At autopsy the most striking cardiac manifestation is a fibrosis of the endocardium and pulmonic valve. That these endocardial changes might be caused by the excess serotonin in the blood is suggested by the fact that the lesions are never seen in the left side of the heart [29] unless there is a patent foramen ovale or other opportunity for right-to-left shunt.[37] Since the lung removes the serotonin by oxidizing it to the inactive 5-hydroxyindole acetic acid,[1] some shunt across the lung would indeed be necessary to permit the serotonin to attack the left side of the heart. The fibrotic lesions in carcinoidosis are not confined to the heart, but may also appear in the region of the tumor. A case has been described with extensive fibrosis of the pelvis. Waldenström [29] also discusses the possibility that congenital endocardial fibroelastosis may be caused by excess serotonin in the fetal circulation. Certainly the bilateral distribution of the lesion in these cases could be related to the shunt normally present in the developing fetal heart. He suggests that the source of the serotonin might be the maternal circulation.

Current observations that the excretion of 5-hydroxyindoleacetic acid is low in patients with hypertensive renal disease suggest the possible relation of this substance to hypertension. Its highly variable effects on blood pressure [38, 39] make it unlikely that serotonin alone is the active agent in hypertension.

The abdominal symptoms in carcinoidosis—colic, borborygmus and diarrhea— which are reported to be diminished by chlorpromazine,[34] can be reproduced by the administration of serotonin or 5-hydroxytryptophane, its precursor. This brings us back to the speculation of Metchnikoff and

[34] Cole, G. B., and Bertino, G. G.: Effect of chlorpromazine on excretion of 5-hydroxyindoleacetic acid in a patient with malignant carcinoid, Proc. Soc. Exper. Biol. and Med. **93**: 100, 1956.

[35] Langfitt, T. W., Hart, E. R., and Marrazzi, A. S.: Relation between cerebral synoptic action of mesialine, indoles, and tranquilizers, Federation Proc. **15**: 495, 1956.

[36] Waldenström, J., and Ljungberg, E.: Studies on the functional circulatory influence from metastasizing carcinoid tumours and their possible relation to enteramine production. I. Symptoms of carcinoidosis, Acta med. Scandinav. **152**: 293, 1955.

[37] McKusick, V. A.: Carcinoid cardiovascular disease, Bull. Johns Hopkins Hosp. **98**: 13, 1956.

[38] Reid, G.: Circulatory effects of 5-hydroxytryptamine, J. Physiol. **118**: 435, 1952.

[39] Page, I., and McCubbin, J. W.: The variable arterial pressure response to serotonin in laboratory animals and man, Circulation Res. **1**: 354, 1953.

more recent suggestions that some of the symptoms of dysentery are caused by amines liberated by gut organisms.

Other possible functions of serotonin which have been proposed include a possible rôle in the production of pulmonary embolism,[40] and a specific rôle in bronchial constriction [41] and in renal function.[8] Erspamer considers serotonin to be a physiologic antidiuretic substance.

The most interesting recent development in this rapidly unfolding story is the relation of serotonin to anaphylactic shock, which is being studied by Fink and by Udenfriend's group. The finding that serotonin is present in lung tissue along with histamine, and that it is liberated into the plasma in anaphylactic shock, adds another dimension to the distressingly incomplete relation between histamine and anaphylaxis.[19]

Much remains to be unraveled in this problem. We have only told the story of how many investigators seeking answers to simple questions about apparently unrelated phenomena have discovered, as in the old fable, that they were all touching the same elephant.

F. J. Borges, M.D.
S. P. Bessman, M.D.

[40] Comroe, J. H., Van Lingan, B., Stroud, R. C., and Roncoroni, A.: Reflex and direct cardiopulmonary effects of 5-hydroxytryptamine, Am. J. Physiol. **173**: 379, 1953.
[41] Herxheimer, H.: Influence of 5-hydroxytryptamide on bronchial function, J. Physiol. **122**: 490, 1953.

REVIEWS

Progress in Hematology. Volume 1. LEANDRO M. TOCANTINS, M.D., Editor, with 27 contributors. 336 pages; 18 × 26 cm. Grune and Stratton, New York. 1956. Price, $9.75.

This volume is intended to acquaint the reader with progress on all fronts in the field of hematology, and future volumes will depend upon response to this one. Actually, this first issue covers sixteen separate hematologic subjects in varying detail; some are presented as rather complete reviews and others as short papers on specific aspects of a disease. All are written by well-known persons and most include extensive bibliographies.

Each of the subjects covered is of interest to both internists and internists especially devoted to blood diseases. However, there have been many recent and important developments which are not mentioned in this book, and it is hoped that the volumes which follow will be more inclusive of the large amount and varied nature of new material in this field.

The contents include gastric intrinsic factor and vitamin B_{12} interrelationships, parenterally administered iron in the treatment of hypochromic anemia, exchange transfusion as a therapeutic measure, the life span of erythrocytes and their post-transfusion survival, abnormal hemoglobins, radioactive colloidal gold in the treatment of severe acquired hemolytic anemia refractory to splenectomy, radioactive phosphorus in the treatment of primary polycythemia, the auto-immune thrombocytopenia, guiding principles in the surgery of hemophilic patients, mechanisms of production of acute fibrinogen deficiencies, local environmental factors affecting hemostasis in bleeding from the gastrointestinal tract, systemic lupus erythematosus and the blood, chemotherapy of human leukemia, the biochemistry and enzymatic activities of leukocytes in health and disease, hematologic recovery from irradiation injury and agammaglobulinemia—congenital, acquired and transient forms.

A. B.

Tuberculosis in Obstetrics and Gynecology. By GEORGE SCHAEFER, M.D., F.A.C.S., F.I.C.S. 307 pages; 22 × 14.5 cm. Little, Brown and Co., Boston. 1956. Price, $8.75.

This small book is divided into three major parts. The section devoted to the principles and treatment of tuberculosis is extremely brief and inadequate, probably intentionally so. The drug treatment portion is but four pages in length and contains six treatment regimens. This presentation might give a false sense of security to the physician who occasionally cares for a tuberculous patient and lead him to the injudicious administration of anti-tuberculosis drugs.

In general, the obstetrical subdivisions are short and in some cases contain observations on one or two patients. These are difficult to evaluate, and the brevity of the discussion does not clarify these sections. The problem of therapeutic abortion in tuberculosis is carefully considered.

The portions dealing with tuberculosis of the breast and gynecologic tuberculosis are consistently more satisfactory than the rest. The principles of diagnosis and the investigative technics employed are clearly stated, and the pathology well presented.

The variants of tuberculous salpingitis are reviewed, with emphasis upon the relationship of genital tuberculosis to sterility.

In the introduction Dr. Schaefer emphasizes the need for a combined medical, surgical, and phthisiologic approach to these patients. His purpose was to present the basic features of tuberculosis in obstetrics and gynecology with brevity and lucidity. The sections are in outline form. The resultant material is too sketchy for the medical student or general practitioner (to whom the book is in part directed) to use in the best interests of the patient. The care of the tuberculous patient must be completely planned in order that the optimum result be obtained. This precludes the casual treatment by a physician who occasionally handles such a problem. The program should be developed jointly among the patient's doctor, a phthisiologist, and the appropriate specialist (obstetrician, etc.), as needed.

This book discusses the diagnostic features of tuberculous infection in the obstetric or gynecologic patient. The observations, in general, were made in the pre-chemotherapy era. The brevity of the discussions, the small numbers of patients included in the obstetrical sections, and the lack of more recent data significantly detract from the value of the book.

J. E. C.

Kapillaren und Interstitium: Morphologie, Funktion, Klinik. Hamburger Symposium vom 29. bis 31. Oktober 1954. Herausgegeben von H. BARTELHEIMER and H. KÜCHMEISTER. 232 pages; 17 × 24 cm. (paper-bound). Georg Thieme Verlag, Stuttgart. 1955. Price, Kartoniert DM 33.60.

This symposium represents an exchange of ideas among 27 investigators from Austria, France, Germany (East and West), Hungary, Netherlands and Switzerland.

Every conceivable aspect of the rôle of capillary activity in the household of the human body is discussed. Numerous methods of studying capillary activity are presented; usually the method as carried out in the normal organism is described first and then its application under conditions of disease is discussed. Among the methods described are those of measuring capillary permeability, capillary resistance, extracellular tissue fluid, of studying interaction between capillaries and interstitium by the employment of isotopes, of measuring intramuscular and subcutaneous tissue fluid pressure (in cantharidin blisters). Throughout, the interaction between capillary function and interstitial tissue receives great emphasis, the two to be considered as members of one system, a relation which is maintained also in the process of inflammation. The question whether proteins can pass through the capillary wall is discussed; the capillary wall as well as cell membranes in general are permeable for intact protein molecules. Also the rôle of hormones in vasomotive activity is considered. Arteriovenous anastomoses, a subject which commenced only recently to occupy a prominent place in the study of circulation physiology, received an ample share of consideration in the present volume, both its morphology and functional aspects being discussed. The structure of the interstitial substances of connective tissue is reviewed on the basis of the latest electron-microscope studies.

At the end of each contribution the reader finds an ample bibliography of the subject. Throughout, this book offers very fascinating reading and permits one to form an idea of the breadth which the subject of capillary function has assumed in the last 40 years. A clean and well-sized print, as usual with Thieme Verlag, and ample illustrations enhance greatly the usefulness of this book.

EDUARD UHLENHUTH

The Lung as a Mirror of Systemic Disease. By ELI H. RUBIN, M.D., Professor of Clinical Medicine, Albert Einstein College of Medicine, Yeshiva University; Director of Pulmonary Diseases, Bronx Municipal Hospital Center; Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital, Consulting Physician in Pulmonary Diseases, Lebanon and Morrisania City Hospitals, New York, N. Y. 288 pages; 29 × 22 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1956. Price, $12.50.

The Lung as a Mirror of Systemic Disease is a new text dealing only with the pulmonary manifestations of systemic diseases. Organization of this material into a single book fills a vacuum previously present in medical literature.

The roentgenologic manifestations of these pulmonary lesions are emphasized but the clinical and pathologic features are adequately discussed. The pathogenesis of all the lesions is clearly presented for a more complete understanding of the disease process.

The material is well organized and illustrated with excellent, though not voluminous, roentgenograms. Many case histories detail the clinical aspects. The bibliography at the end of each chapter is extensive and complete with the most recent references.

This book will be a useful reference for internists and radiologists.

JOHN M. DENNIS, M.D.

Handbook of Pediatric Medical Emergencies. 2nd Ed. By ADOLPH G. DESANCTIS, M.D., with the collaboration of CHARLES VARGA, M.D., and ten contributors. 389 pages; 14.5 × 22.5 cm. The C. V. Mosby Co., St. Louis, Mo. 1956. Price, $6.25.

This popular book gives specific instructions for the treatment of many kinds of emergencies occurring in the United States. There are good illustrations of the technics, ample references, and no controversial discussions. The type, binding, and outline presentation are well adapted for quick reference and for the arduous use books get in an emergency room. A physician who deals with these emergencies is sure to disagree with many of the instructions and modify many others to suit individual patients. The book must not be used as a recipe-book or a substitute for clinical judgment.

G. A. C.

Excitability of the Heart. By CHANDLER MCC. BROOKS, Ph.D., BRIAN F. HOFFMAN, M.D., E. E. SUCKLING, M.Sc., M.E.E., and OSCAR ORIAS, M.D. 373 pages; 14 × 22 cm. Grune & Stratton, New York. 1955. Price, $6.50.

In the foreword to this text, Dr. Carl J. Wiggers states, "The monograph will, I predict, be considered a classic by physiologists." In this monograph, the authors have presented the results of their own studies, reviews of earlier studies and the many unsolved problems which still remain. The study of the excitability and the excitatory process is of fundamental importance in the understanding of cardiac function. The present concepts of the initiation and propagation of activity in living tissue are discussed. The methodologies and apparatus developed for the study of excitability and cardiac response, including technics applicable to cellular elements are described in detail. The changes in cardiac excitability which occur during the cardiac cycle are defined with a description of the newer phenomena "dips" in excitability. The reactions of the heart to various drugs, heat and cold, humoral mediators and hormones are also presented. Of particular interest is the presentation of the studies of the authors on transmembrane potentials of cardiac muscle. There

are excellent discussions of the problems of fibrillation, including the production and nature of fibrillation, defibrillation and the prevention of fibrillation.

This is an authoritative text on the problems on cardiac excitability. It is well written considering the complexity of the subject. The prediction of Dr. Carl J. Wiggers in the foreword should be fulfilled. The text should be available as a reference volume for all of those interested in the problems of the excitability of the heart. This should include students, basic scientists, surgeons and internists.

L. S.

BOOKS RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Allergy and Asthma: The Relationship Between Allergy and the Autonomic Nervous System, Especially the Parasympathicus. By MASUICHI TAKINO, M.D., Former Lecturer of Internal Medicine, Kyoto University, etc.; and YOSHITADA TAKINO, M.D., Research Assistant of Dainipponzōki Institute for Medical Research. 249 pages; 26 × 19 cm. 1956. Maruzen Co., Ltd., Tokyo.

Blood Volume and Contractile Protein in Heart Muscle. World Trends in Cardiology: III. Edited by ARTHUR S. CAIN, JR., M.D., College of Physicians and Surgeons, Columbia University, New York. 131 pages; 21.5 × 14 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.50.

Bone Structure and Metabolism: Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. 299 pages; 21 × 14 cm. 1956. Little, Brown & Company, Boston. Price, $8.00.

Cardiovascular Diagnosis and Therapy. World Trends in Cardiology: IV. Edited by ARTHUR S. CAIN, JR., M.D., College of Physicians and Surgeons, Columbia University, New York. 95 pages; 21.5 × 14 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.85.

Cardiovascular Epidemiology. World Trends in Cardiology: I. Edited by ANCEL KEYS, Ph.D., University of Minnesota, Minneapolis; and PAUL D. WHITE, M.D., Harvard Medical School, Boston. 193 pages; 21.5 × 14 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $4.75.

Cardiovascular Surgery: Panel Discussions. World Trends in Cardiology: II. Edited by HELEN B. TAUSSIG, M.D., School of Medicine, Johns Hopkins University, Baltimore; and ARTHUR S. CAIN, JR., M.D., College of Physicians and Surgeons, Columbia University, New York. 65 pages; 21.5 × 14 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $2.00.

Clinical Unipolar Electrocardiography. 3d Ed. By BERNARD S. LIPMAN, A.B., M.D., F.A.C.P., Instructor in Medicine, Emory University School of Medicine, etc.; and EDWARD MASSIE, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine, etc. 397 pages; 22.5 × 14.5 cm. 1956. The Year Book Publishers, Chicago. Price, $7.50.

Examination of the Nervous System: A Student's Guide. By A. THEODORE STEEGMANN, M.D., Professor of Medicine (Neurology), University of Kansas School of Medicine, Kansas City, Kansas. 164 pages; 19.5 × 13.5 cm. (paper-bound). 1956. The Year Book Publishers, Inc., Chicago. Price, $3.75.

Handbook of Pediatric Medical Emergencies. 2nd Ed. By ADOLPH G. DESANCTIS, M.D., Professor of Pediatrics and Chairman of the Department of Pediatrics, Post-Graduate Medical School, New York University-Bellevue Medical Center, etc.; with the collaboration of CHARLES VARGA, M.D., Portland, Oregon, and 10 contributors. 389 pages; 22.5 × 14.5 cm. 1956. The C. V. Mosby Company, St. Louis. Price, $6.25.

The Happy Life of a Doctor. By ROGER I. LEE, M.D. 278 pages; 21 × 14 cm. 1956. Little, Brown and Company, Boston. Price, $4.00.

Histological Appearances of Tumours, With a Consideration of Their Histogenesis and Certain Aspects of Their Clinical Features and Behaviour. By R. WINSTON EVANS, T.D., B.Sc. (Lond.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), Consultant Pathologist, United Liverpool Hospitals (David Lewis Northern Hospital and St. Paul's Eye Hospital), etc. 773 pages; 25.5 × 19 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $17.00.

Instrumental Methods in Cardiac Diagnosis. World Trends in Cardiology: V. Edited by LOUIS N. KATZ, M.D., Michael Reese Hospital, Chicago; and ARTHUR S. CAIN, JR., M.D., College of Physicians and Surgeons, Columbia University, New York. 100 pages; 21.5 × 14 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department, Harper & Brothers, New York. Price, $3.85.

The Management of Tuberculosis: Symposium. Editor: IRVING J. SELIKOFF, M.D., Associate Attending Physician for Thoracic Diseases, The Mount Sinai Hospital, New York; contributions to the Symposium by members of the staff of The Mount Sinai Hospital, New York. 646 pages; 26 × 17.5 cm. 1956. The Journal of The Mount Sinai Hospital, New York, publisher. Price, $5.00.

The Merck Manual of Diagnosis and Therapy. 9th Ed. Editorial Board: CHARLES E. LYGHT, M.D., Editor; WILLIAM P. BOGER, M.D., GEORGE A. CARDEN, M.D., AUGUSTUS GIBSON, M.D., and DICKINSON W. RICHARDS, M.D. 1,870 pages; 17.5 × 11 cm. 1956. Merck & Co., Inc., Rahway, N. J. Price, Regular edition, $6.75; deluxe edition, $9.00.

Official History of the Canadian Medical Services, 1939–1945. Volume One: *Organization and Campaigns.* Edited by W. R. FEASBY, B.A., M.D., Lieutenant-Colonel, R.C.A.M.C., Supplementary Reserve, Lecturer in Physiology, University of Toronto; illustrated with paintings and photographs by Canadian war artists and photographers; maps drawn by CAPTAIN C. C. J. BOND. 568 pages; 26 × 17 cm. 1956. Edmond Cloutier, C.M.G., A.O., D.S.P., Ottawa, 1956, Queen's Printer and Controller of Stationery. Price, $5.00 postpaid; obtainable from Superintendent of Government Publications, Department of Public Printing and Stationery, Ottawa, Canada.

Paper Electrophoresis: Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and ELAINE C. P. MILLAR, A.H.-W.C., A.R.I.C. 224 pages; 21 × 14 cm. 1956. Little, Brown and Company, Boston. Price, $6.75.

The Person Behind the Disease. By JULIUS BAUER, M.D., F.A.C.P., Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles, etc. 136 pages; 22.5 × 14 cm. 1956. Grune & Stratton, New York. Price, $3.50.

Pharmacology and Oral Therapeutics: A Textbook for Students and Practitioners. 11th Ed. By EDWARD C. DOBBS, B.S., D.D.S., F.A.C.D., Professor of Pharmacology and Therapeutics, Dental School, University of Maryland. 579 pages; 22.5 × 14 cm. 1956. The C. V. Mosby Company, Saint Louis. Price, $9.00.

Practical Pediatric Dermatology. By MORRIS LEIDER, M.D., Associate Professor of Dermatology and Syphilology, New York University Post-Graduate Medical School, etc. 433 pages; 25.5 × 17.5 cm. 1956. The C. V. Mosby Company, Saint Louis. Price, $10.50.

Principles of Clinical Electrocardiography. By MERVIN J. GOLDMAN, M.D., Assistant Chief of the Medical Service and Cardiologist, Oakland Veterans Administration Hospital, Oakland. 310 pages; 25.5 × 17.5 cm. (paper-bound). 1956. Lange Medical Publications, Los Altos, California. Price, $4.50.

Psychologic Aspects in the Care of Infants and Children: Report of the Twenty-first Ross Pediatric Research Conference. 90 pages; 23 × 15 cm. (paper-bound). 1956. Issued by Ross Laboratories (formerly M & R Laboratories), Columbus, Ohio. Free on request.

Pulmonary Circulation and Respiratory Function: A Symposium Held at Queen's College, Dundee, University of St. Andrews, 1956. 44 pages; 25 × 18.5 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $2.00.

Refresher Course for General Practitioners: Specially Commissioned Articles from the British Medical Journal. Third Collection, April 1952 to September 1953 (Fully Revised). 548 pages; 22.5 × 14.5 cm. 1956. British Medical Association, London. Price, 25s. net.

Services for Children with Hearing Impairment: A Guide for Public Health Personnel. Prepared by the COMMITTEE ON CHILD HEALTH OF THE AMERICAN PUBLIC HEALTH ASSOCIATION, 1956. 124 pages; 23 × 15.5 cm. (paper-bound). 1956. The American Public Health Association, Inc., New York. Price, $1.50.

Services for Children with Vision and Eye Problems: A Guide for Public Health Personnel. Prepared jointly by the COMMITTEE ON CHILD HEALTH OF THE AMERICAN PUBLIC HEALTH ASSOCIATION and the NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS, 1956. 112 pages; 23 × 15.5 cm. (paper-bound). 1956. The American Public Health Association, Inc., New York. Price, $1.50.

Strahlendosis und Strahlenwirkung. By B. RAJEWSKY; unter mitarbeit von K. AURAND, O. HUG, H. MERGLER, H. MUTH, H. PAULY, A. SCHRAUB, E. SIX and I. WOLF. 280 pages; 21.5 × 15 cm. (leather-bound). 1956. George Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, DM 36.–

Symposium on Vitamin Metabolism: Proceedings of a Symposium Held Under the Auspices of The University of Texas and The National Vitamin Foundation, Incorporated, New York City, March 6, 1956. Nutrition Symposium Series Number 13. Contributors: G. M. BROWN, J. J. BURNS, I. C. GUNSALUS, L. M. HENDERSON, J. HURWITZ, C. A. NICHOL, S. OCHOA, G. W. E. PLAUT and L. D. WRIGHT. 118 pages; 27 × 19.5 cm. (paper-bound). 1956. The National Vitamin Foundation, Incorporated, New York. Price, $2.50.

ERRATUM

In the article entitled "The Metabolism of Folic Acid in Cirrhosis," by James H. Jandl, M.D., and Arnold A. Lear, M.D., which appeared in the December, 1956 issue of the ANNALS OF INTERNAL MEDICINE, an essential line was omitted from the legend of figure 3 on page 1035. The correct wording of this legend is as follows:

FIG. 3. Relation between intake and urinary excretion of folic acid in two normal men. Solid black circles represent the daily urinary output of folic acid at various dosages of PGA administered subcutaneously. Empty circles depict the urinary excretion of folic acid following orally administered PGA. Empty triangles indicate the excretion of folic acid after the ingestion of conjugated folic acid (yeast A), and empty squares, the daily output following the ingestion of deconjugated yeast folic acid (yeast B). The mean values are represented in each instance by horizontal bars. All preparations were administered preprandially in thrice-divided doses. It should be noted that a log-log scale has been employed.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1957–58

In accordance with provisions of the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1957–58, are herewith announced to the Fellows and Masters of the College:

President-Elect ..... Dwight L. Wilbur, San Francisco, Calif.
First Vice President ..... Herbert K. Detweiler, Toronto, Ont.
Second Vice President ..... Charles A. Doan, Columbus, Ohio
Third Vice President ....Lemuel C. McGee, Wilmington, Del.

Regular elections will take place at the 1957 Annual Session, Boston, Mass., on April 11, 1957, 2:00 P.M., the date of the Annual Business Meeting, at Mechanics' Building.

Election of nominees shall be by the Fellows and Masters. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,

Eugene B. Ferris, Chairman, Atlanta, Ga.
Philip S. Hench, Rochester, Minn.
Fay F. Farquharson, Toronto, Ont.
R. Carmichael Tilghman, Baltimore, Md.
Robert H. Ebert, Cleveland, Ohio

Notice of Proposed Amendment to the By-Laws of the American College of Physicians

Fellows and Masters of the American College of Physicians are hereby informed that the Board of Regents approved on November 10–11, 1956, the following amendment to the By-Laws of the College and will recommend its adoption at the next Annual Business Meeting at Boston, Mass., April 11, 1957.

By-Laws, Article V, Add Paragraph (c) and Renumber Two Succeeding Paragraphs, (d) and (e)

"(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions."

New Life Members

The College acknowledges with pleasure the following Fellows as new Life Members:

Dr. Seymour S. Balkin, Forest Hills, N. Y.
Dr. Martin H. Boldt, Louisville, Ky.
Dr. Lyman C. Boynton, Rochester, N. Y.
Dr. Heinz B. Eisenstadt, Port Arthur, Tex.
Dr. David A. Newman, Palm Beach, Fla.
Dr. Sheldon Schwartz, Queens Village, N. Y.
Dr. Ross Van V. Taylor, Jackson, Mich.

Books Donated to the College Library of Publications by Members

The College gratefully acknowledges receipt of the following autographed books from Fellows of the College to the Memorial Library of the College:

Julius Bauer, M.D., F.A.C.P., Los Angeles, Calif., *The Person Behind the Disease,* published by Grune & Stratton, Inc., New York and London, 1956, 136 pages.

Bernard S. Lipman, M.D., F.A.C.P., Atlanta, Ga., *Clinical Unipolar Electrocardiography,* published by The Year Book Publishers, Inc., Chicago, Third Edition, 1956, 397 pages, illustrated; co-authored with Edward Massie, M.D., F.A.C.P.

Roger I. Lee, M.D., M.A.C.P., Boston, Mass., *The Happy Life of a Doctor,* published by Little, Brown and Company, Toronto, 1956, 278 pages.

Arthur Ruskin, M.D., F.A.C.P., Galveston, Texas, *Classics in Arterial Hypertension,* published by Charles C. Thomas, Springfield, Ill., 1956, 358 pages, illustrated.

Edward A. Strecker, M.D., F.A.C.P., Philadelphia, Pa., *Their Mothers' Daughters,* published by J. B. Lippincott Company, Philadelphia and New York, 1956, 256 pages.

The Dr. George Morris Piersol Rehabilitation Center of the Hospital of the University of Pennsylvania

The Rehabilitation Center of the Hospital of the University of Pennsylvania will be enlarged and remodeled to increase its services to disabled and physically handicapped persons and its facilities for teaching and research in rehabilitation. This construction program will double the Center's present floor space. It is expected to be concluded by the latter part of 1957.

The Center will be named in honor of Dr. George Morris Piersol, M.A.C.P., Dean of the Graduate School of Medicine and Professor Emeritus of Physical Medicine and Rehabilitation. Dr. Piersol is a former President of the American College of Physicians, and for 25 years was its Secretary General. He was the first Chairman of the University's Rehabilitation Commission.

Dr. Walter Beckh, F.A.C.P., San Francisco, Calif., has been recently promoted to Clinical Professor of Medicine at Stanford University School of Medicine.

Dr. Carl J. Wiggers, F.A.C.P., Professor Emeritus, Western Reserve University School of Medicine, Honorary Professor, Frank E. Bunts Educational Institute, and Editor, *Circulation Research,* has received the degree of Doctor of Medicine Honoris Causa from the University of Brussels. He was awarded a gold medal by the Belgian Academy of Medicine, and has been elected President of the Inter-American Congress of Cardiology.

Dr. Paul Dudley White, M.A.C.P., Emeritus Professor of Medicine, Harvard Medical School, Boston, delivered the Thirty-second Hermann M. Biggs Memorial Lecture under the auspices of the Committee on Public Health of the New York Academy of Medicine, on the evening of Feb. 7, 1957, in the Academy Building. His subject was "The Relation of Ways of Life to Heart Disease." This was the second time that Dr. White presented the Biggs Memorial Lecture in the series sponsored by the Committee on Public Health, the previous occasion being in 1940 when he spoke on "Heart Disease—A World Problem."

New Film—The Metabolic Insufficiency Syndrome: Diagnosis and Treatment

Smith, Kline & French Laboratories, Philadelphia, has recently completed a new film under the title, The Metabolic Insufficiency Syndrome: Diagnosis and Treatment. This film will be made available to individuals and small groups on loan, and without charge to professional medical groups and individual physicians. The film can be obtained either through one of their representatives or by writing to Mr. Daniel O. Hastings, III, Medical Film Center, Smith, Kline & French Laboratories, Philadelphia 1, Pa. They request four weeks' advance notice and an alternate showing date whenever possible.

Dr. William B. Bean, F.A.C.P., Iowa City, Iowa, gave the Harro Woltman lecture, and participated in the Harro Woltman Day celebrations at Mansfield, Ohio, on October 10. On October 16, Dr. Bean delivered the feature lecture at the Regional Meeting of the American College of Physicians at Albuquerque, N. M., his title being "Useful Lessons from Rare Diseases." He also addressed the banquet on the subject, "Careers in Medicine." On October 17, Dr. Bean delivered two addresses before the meeting of the Southwestern Medical Association, "Precordial Noises Heard at a Distance from the Chest" and "The Clinical Importance of Vascular Lesions of the Skin." Still further, on November 1, 2, and 3, Dr. Bean was in attendance at the 69th Meeting of the American Clinical and Climatological Association, and delivered a paper entitled "Report of a Patient with Metastatic Carcinoid and Hyperserotoninemia." He also acted as Moderator of a Symposium on Aspects of the Liver and Hormone Regulation, before the American Association for the Study of Liver Diseases on November 8.

Dr. Raymond Sheets, F.A.C.P., Iowa City, Iowa, has been elected to the Council of the Central Society for Clinical Research for a term of three years, 1957–1960.

Dr. Lewis E. January, F.A.C.P., State University of Iowa College of Medicine, has received a continuation of the grant from the American Heart Association for support of the Cardiac-in-Agriculture Demonstration Project being carried out in Washington County, Iowa. The amount of the grant is $1,250.

Dr. Paul M. Seebohm, F.A.C.P., Associate Professor of Medicine at the State University of Iowa College of Medicine, has received a grant of $1,000 from the Winneshiek County Tuberculosis and Health Association of Iowa for continuation of his studies in the field of pulmonary physiology.

Ann Arbor Selected as Site for $10,000,000 Research Center

Parke, Davis & Company has announced the selection of Ann Arbor as the site for its new $10,000,000 Medical Research Center.

Proximity to the firm's Detroit headquarters, accessibility by air and land, and availability of the University's cultural and educational facilities were factors in the selection of the site. The new structure is expected to be completed by early 1959, and will supplement the firm's present research facilities, which include the original laboratory that was the first in America to be erected by any commercial institution solely for scientific research.

Fellowships Available in Field of Cerebral Palsy

Twenty fellowships for specialized training in working with cerebral palsied and other severely handicapped persons are available through the National Society for Crippled Children and Adults, 11 S. LaSalle Street, Chicago 3, Illinois. Applications should be submitted by March 15, 1957. The training will be held June 17 to July 12 at the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center, New York City. Stipends are $300 each covering tuition and a moderate amount of living expenses. Six points of academic credit at the graduate level will be given to those who successfully complete the course.

5th Postgraduate Course by the American Diabetes Association

The American Diabetes Association conducted its 5th Postgraduate Course in Diabetes and Basic Metabolic Problems at The Ohio State University Health Center, Columbus, Ohio, January 30 to February 1, 1957. Dr. George J. Hamwi, F.A.C.P., and Dr. Thomas P. Sharkey, F.A.C.P., were Director and Associate Director, respectively. Most of the Faculty were Fellows of the American College of Physicians. The Course was divided among the following subjects: Pathophysiology of Diabetes Mellitus, Diagnosis of Diabetes Mellitus, Clinical Management of Diabetes Mellitus, Oral Hypoglycemic Agents, Objectives of Treatment in Diabetes Mellitus, Conditions Complicating Diabetes Mellitus, Hypoglycemia, and Chronic Complications of Diabetes Mellitus.

Dr. Charles E. Kossmann, F.A.C.P., Associate Professor of Medicine at New York University College of Medicine, was a guest speaker on the Program of the Third Postgraduate Assembly on Cardiovascular Diseases, sponsored by the Bernalillo County Heart Clinic, Bernalillo County Heart Association, and the New Mexico Heart Association, held at Albuquerque, New Mexico, November 17, 1956.

Dr. Simon S. Leopold, F.A.C.P., Philadelphia, has been Medical Director of the National Disease and Therapeutic Index since its inception in January, 1956. Recently, the following Fellows of the American College of Physicians accepted membership on advisory committees of this program which is designed to provide continuous statistical information for study of the reasons why patients see doctors and the types of treatment they receive: Dr. George Morris Piersol, M.A.C.P., Dean, University of Pennsylvania Graduate School of Medicine, Philadelphia; Dr. J. Murray Kinsman, F.A.C.P., Dean, University of Louisville School of Medicine, Louisville; Dr. George A. Wolf, Jr., F.A.C.P., Dean, University of Vermont College of Medicine, Burlington.

Dr. William Paul Thompson, F.A.C.P., was elected Chairman of the Section on Clinical Cardiology of the American Heart Association at its annual meeting at Cincinnati, October 1956. Dr. Clifford B. Cherry, F.A.C.P., was elected to the Committee on Community Program Evaluation; Dr. Louis E. Martin, F.A.C.P., was reëlected a Vice President; Dr. George C. Griffith, F.A.C.P., was elected Secretary of the Scientific Council.

U. S. Atomic Energy Commission Special Fellowships

The Atomic Energy Commission offers fellowships which provide advanced training and on-the-job experience in the field of Industrial Medicine, particularly

in relation to the atomic energy industry. The selection of Fellows is made by the Atomic Energy Commission on recommendation of the Committee on A.E.C. Fellowships in Industrial Medicine. For the academic year 1957–1958, eight Fellowships will be available. The stipend during a Fellowship or academic year is $5,000, usually divided into a minimum of 9 or a maximum of 12 equal payments, depending upon the starting date elected by the Fellow.

For detailed information concerning qualifications, fellowship activities, conditions of appointment and location of work, address: A.E.C. Fellowships in Industrial Medicine, Attn: Dr. Henry A. Blair, Atomic Energy Project, University of Rochester School of Medicine and Dentistry, Rochester 20, N. Y.

Dr. Saul A. Schwartz, (Associate), Assistant Professor of Medicine and Gastroenterology at the New York Medical College, presented a paper on "New Approach to the Management of Peptic Ulcer by Inducing Sustained Gastric Inacidity" at the annual meeting of the American College of Gastroenterology, New York, October 15, 1956. Dr. Schwartz was also a panelist in a discussion on the subject of ulcerative colitis, held at the New York Medical College-Metropolitan Hospital Center, October 18, 1956, under the auspices of the American College of Gastroenterology.

The cardiovascular service group at the University of Texas, Dr. George R. Herrmann, F.A.C.P., Dr. Milton R. Hejtmancik, F.A.C.P., Dr. Zang Z. Zao, Dr. J. R. Wright, and Dr. Allen Shields, presented four papers on the program at the V Congreso Inter-Americano de Cardiologia and two papers by title and two exhibits, and received diplomas of achievement. In contributions to the program the Cubans ranked first, the Mexicans second and the Texans third.

Dr. George R. Herrmann, Director of Latin-American Relations in Medicine for the University of Texas Medical Branch, was elected to the Council of Honor for meritorious, scientific services contributed to the IACS. Others elected to this five-man Council of Honor are Dr. Paul Dudley White, M.A.C.P., of Boston, Dr. Pedro Cossio of Buenos Aires, Argentina, Dr. Ramon Aixala of Havana, Cuba, and Dr. Teofilo Ortiz of Mexico, D. F.

Dr. Seymour S. Balkin, F.A.C.P., has been appointed Assistant Professor of Clinical Medicine, State University of New York College of Medicine at New York City.

Among the new officers of the New York Allergy Society are Dr. Samuel J. Prigal, F.A.C.P., President; Dr. Joseph H. Fries, F.A.C.P., Treasurer; and Dr. Sheppard Siegal, F.A.C.P., Assistant Secretary-Treasurer.

Dr. C. Wilmer Wirts, Jr., F.A.C.P., and Dr. Malcolm W. Miller, F.A.C.P., have been elected Director and Assistant Director, respectively, of the Philadelphia (Pa.) County Medical Society's Postgraduate Institute, which will be held in Philadelphia, March 19–22, 1957.

The University of Pennsylvania is the recipient of grants totalling $550,000 from the United States Public Health Service to assist in the construction of health research facilities. One grant of $400,000 was made toward the construction of a new research laboratory wing on the School of Medicine building and for research facilities in two other new medical structures. These are a part in the initial steps

in a comprehensive, long range program for the extension and integration of research facilities in the health sciences at the University. Total cost of this research construction will be $3,200,000, of which one-half is expected to be borne by the Federal Government over a three-year period.

Dr. Howard Wakefield, F.A.C.P., Chicago, has been appointed for a three-year term as official representative and consultant on behalf of the American College of Physicians to the American Occupational Therapy Association, Medical Advisory Council.

University of Minnesota Announces Course for Internists

The University of Minnesota will conduct a CONTINUATION COURSE IN RECENT ADVANCES IN INTERNAL MEDICINE FOR INTERNISTS at the Center for Continuation Study on the University Campus, March 4–6, 1957. Fundamental advances related to clinical practice will be stressed. Areas to be covered include infectious diseases, neurology, cardiology, and gastroenterology. Among guest faculty members are Dr. Carleton B. Chapman, F.A.C.P., Professor of Medicine, Southwestern Medical School, Dallas, Texas, and Dr. Max B. Lurie, Professor of Experimental Pathology, Henry Phipps Institute, Philadelphia, Pa. The Course will be directed by Dr. Wesley W. Spink, F.A.C.P., Professor of Medicine at the University of Minnesota, and a Governor of the American College of Physicians.

International Congress of Internal Medicine to Be Held in America, 1958

At its November meeting the Board of Regents of the American College of Physicians voted to extend an invitation to the International Society of Internal Medicine to hold its 1958 meeting in the United States. This Society was organized in 1948 and has held four biennial Congresses: in Paris, London, Stockholm and Madrid. The former presidents of the Society have been Professor A. Gigon of Basel, Switzerland, and Professor Nanna Svartz of Stockholm, Sweden. Sir Russell Brain, Hon. F.A.C.P., has been elected president for the next four years. The presidents of the four Congresses have been Professor André Lemierre of Paris, Sir Russell Brain, Professor Svartz and Professor C. Jimenez Diaz of Madrid. At the recent Congress in Madrid forty-seven countries were represented and the attendance numbered about 1300.

Although at this time only 120 Fellows of the American College of Physicians are members of the Society, most of these have attended one or more of the Congresses. Among the Fellows of the College who have made presentations have been Drs. Philip S. Hench, Walter L. Palmer, William S. Middleton, T. Grier Miller, Sara Jordan, Charles A. Flood and Frank N. Allan.

The stated objectives of the Society are to advance medical knowledge, to promote the education of younger members of the profession and to encourage friendship among physicians of different countries. Furthermore, the Society, like the American College of Physicians, includes among its members those interested in all branches of internal medicine.

It is anticipated that incident to the 1958 meeting in the United States, many Fellows of the College will now seek membership. Applications should be sent to I S I M, American College of Physicians, 42nd and Pine Streets, Philadelphia, for consideration by the American Committee of the Society.

OBITUARIES

Recent Deaths of A.C.P. Members

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. Charles Edward Boynton, F.A.C.P., Ponte Vedra Beach, Fla., Nov. 22, 1956
Dr. Stephen Horace Curtis, F.A.C.P., Troy, N. Y., Aug. 20, 1956
Dr. John Severy Hibben, F.A.C.P., Pasadena, Calif., Sept. 30, 1956
Dr. Sidney Lechner, (Associate), New York, N. Y., date unknown
Dr. Clifford Hayes Mack, (Associate), Lake Ariel, Pa., Nov. 14, 1956
Dr. George Elliott Woodford, (Associate), Short Hills, N. J., May 24, 1954
Dr. Israel Sidney Zaur, F.A.C.P., Bridgeport, Conn., July 18, 1956

The College headquarters at 4200 Pine St., Philadelphia 4, Pa., would appreciate it if members and readers send in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. HAROLD LINDSAY AMOSS

Dr. Harold L. Amoss, F.A.C.P., was born in Princeton, Ky., in 1886, the son of the late David A. and Carolyn Lindsay Amoss. He received his Bachelor and Masters degrees at the University of Kentucky, and in 1911 his medical degree from Harvard Medical School. He then studied at George Washington University where he was awarded the degree of Doctor of Public Health in 1912. He received an honorary degree of Doctor of Science at George Washington in 1922.

He became an Associate Member of the Rockefeller Institute and was Instructor of Preventive Medicine at Harvard from 1912 to 1922. It was during this period that he engaged in research in infectious diseases, particularly poliomyelitis. World War I interrupted this work and he joined the Army Medical Corps, serving overseas from 1918 to 1919 with the rank of Major.

He went to Johns Hopkins Hospital in 1922 and remained until 1930, serving as Associate Professor of Medicine at the medical school and continuing his work in infectious diseases. He was appointed Professor of Medicine at Duke University Medical School in 1930 and remained there until 1933. For a brief time in 1932, he was associated with the Peking University Medical College in China.

Dr. Amoss entered private practice in Greenwich in 1933 and remained in active practice until his death. During World War II, he was Chairman of the Medical Advisory Board for the Selective Service System of Fairfield (Conn.) County. He was a Mason, a member of the local, county and state medical societies, and the American Medical Association. He was a member of the American Society for Clinical Investigation, Association of American Physicians, American Society of Experimental Pathology, American Association for the Advancement of Science, American College of Physicians, American Society for Experimental Biology and Medicine, and the American Society of Immunologists. He served as consultant for Greenwich Hospital, Grasslands Hospital, Valhalla, New York; White Plains Hospital, White Plains, New York; and the United Hospital, Port Chester, New York.

Dr. Amoss suffered a coronary occlusion complicated by pyelonephritis and died on November 2, 1956, at the age of 70. Surviving are his wife, Marguerite Moore Amoss, and two sons, Dr. Harold L. Amoss, Jr., of Kabul, Afghanistan, and Dudley M. Amoss of Salt Lake City, Utah, a sister Mrs. Rawles Moore of Medford, Oregon, and seven grandchildren.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut

DR. WILLIAM POPE BAKER

Dr. William Pope Baker was born in Zebulon, Ga., June 3, 1893, the son of William Battle and Maude Stillwell Baker. He attended Tech High School and the Peacock School and had premedical training at the University of Pennsylvania for two years. He was graduated with a degree of Doctor of Medicine from Emory University in 1920, and served an internship at Grady Hospital in 1920–21. His postgraduate work was done at the Massachusetts General Hospital, Peter Bent Brigham Hospital, the Johns Hopkins Hospital, and at the Mayo Clinic. He specialized in Therapeutic Radiology.

He began his practice in Atlanta and was a pioneer in the field of therapeutic radiology in this territory, maintaining an office at Piedmont Hospital until 1936, when he retired because of Parkinson's disease.

Dr. Baker was a member of the Fulton County Medical Society, the Medical Association of Georgia, the American Medical Association, Southern Medical Association, and the Radiological Society of North America. He became a Fellow of the American College of Physicians in 1929.

Dr. Baker was a member of St. Mark's Methodist Church, the Kappa Sigma Chi Medical Fraternity and the Mystic Shrine.

Although he was an invalid for almost twenty years, he bore his misfortune uncomplainingly. He died in Atlanta on July 12, 1956. He is survived by his wife, Maude Stilwell Baker, who resides at 979 Springdale Road, Atlanta, Ga.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. SAMUEL SYLVESTER BERGER

Dr. Samuel Sylvester Berger, F.A.C.P. (1925), Cleveland, Ohio, was born in Kis-Dobra, Hungary, April 14, 1884. After emigrating from Hungary to this country, he entered Western Reserve University School of Medicine, receiving his M.D. degree in 1904, and was a member of the Alpha Omega Alpha honorary medical fraternity. He served his internship at Mt. Sinai Hospital at Cleveland, Ohio and then served varying periods of time in postgraduate work in Berlin, Munich, Vienna, Zurich and London during the years 1906, 1922, and again in 1936. His entire professional life other than for these periods abroad, was spent in Cleveland in close association with Mt. Sinai Hospital, where he was Chief of Medicine from 1923 to 1945. He was one of the first physicians in Cleveland to become interested in gastroscopy, going to Chicago for special training with Dr. Schindler, and from 1947 to the time of his death, he was consultant in charge of Gastroenterology at the Mt. Sinai Hospital. At the time of his death, he was planning to attend an International Conference on Gastroenterology in Europe as a delegate from this country. Together with Dr. B. S. Kline, Dr. Berger was awarded the Silver Medal of the American Medical Association in 1925 for a scientific exhibit.

Dr. Berger served as Chairman of the Clinical and Pathological Section of the Cleveland Academy of Medicine and maintained membership in the American Heart Association, the American Diabetes Association, the American Gastroenterological

Association, and was a Diplomate of the American Board of Internal Medicine. Dr. Berger also was a member of the American Medical Editors Association and of the American Association for the Study of Internal Secretions.

Death occurred on September 18, 1956, of a myocardial infarction. This well-known, well-beloved physician in Cleveland is survived by his wife, Mrs. Vera Grossman Berger, and three children, Peter of Washington, D. C., Mrs. Howard Sirak of Columbus, Ohio, and Miss Barbara Berger of Chicago, and there are two grandchildren. The Fellows and Associates of the American College of Physicians, as well as Dr. Berger's friends in Cleveland, mourn his untimely death, and express to the family deepest sympathy.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. CHARLES KETTIG BERLE

Charles Kettig Berle, M.D., Colonel (Retired), Medical Corps, U. S. Army, died on September 13, 1956, in San Francisco after a lingering illness (hypertensive cardiovascular disease).

Dr. Berle was born in Kentucky on October 21, 1890. He attended the University of Louisville, School of Medicine, Class of 1914. His further studies at the Army Medical School were completed before his internship (1914–1916) at the Louisville City Hospital. Dr. Berle's career from that time on was devoted to work with the Army, and among his assignments were duty at the Sternberg General Hospital in the Philippine Islands, United States Army Ambulance Service with the French Army during World War I. After his war service he was attached to the Station Hospital of the United States Military Academy at West Point, and later transferred to the Walter Reed General Hospital in Washington. Letterman Hospital in San Francisco was fortunate in having the guidance of this able man until October, 1947 when he retired because of physical disability.

Dr. Berle was a Diplomate of the American Board of Internal Medicine, and since 1930 had been a Fellow of the American College of Physicians. His career as a physician was a long and useful one—not only in the service of his country, but it touched the lives of many civilians and was an inspiration and example to all of those with whom he came in contact.

STACY R. METTIER, M.D., F.A.C.P.,
Governor for Northern California and Nevada

DR. HAROLD OTIS COZBY

Dr. Harold Otis Cozby of Chula Vista, Calif., died on August 28, 1956, of coronary thrombosis. Born in Van Zandt County, Texas, on Oct. 8, 1901, Dr. Cozby received an A.B. degree from the University of Texas in 1921; his M.D. degree from the University of Texas School of Medicine at Galveston in 1924; and did post-graduate study in neurology and psychiatry at the U. S. Naval Medical School, George Washington Medical School and American University in Washington, D. C.

After serving a short term as Assistant Physician at the Bingham State Hospital (1924–1925), Dr. Cozby entered the U. S. Naval Medical Corps in 1925, rising to the rank of Captain. Immediately after World War II, Dr. Cozby left the Naval Service and resumed private practice. A Diplomate of the American Board of Internal Medicine, and of the American Board of Psychiatry and Neurology, he practiced neuro-psychiatry in San Diego County, serving on the staff of Mercy Hospital, the San Diego County General Hospital, and the Vista Hill Sanitorium at Chula Vista. He was also a member of the American Medical Association, American Psychiatric Association, American Society of Mental Hygiene, American Asso-

ciation of Military Surgeons, Washington Nervous and Mental Disease Society, Washington Pathological Society, American Academy of Neurology, and in 1935 became a Fellow of the American College of Physicians.

Dr. Cozby retired from active practice in 1954, and was living in retirement in his home at 3 North Second St., Chula Vista, Calif., at the time of his death.

GEORGE C. GRIFFITH, M.D., F.A.C.P.,
Governor for Southern California

DR. LOUIS WINFIELD KOHN

Dr. Louis Winfield Kohn died on August 16, 1956, New York City, of a heart attack.

Dr. Kohn was born in 1888 in New York City. He received his degree of Doctor of Medicine in 1910 at the University of Maryland School of Medicine.

During Dr. Kohn's early career he served variously as Assistant in Medicine at the Johns Hopkins Hospital, Baltimore; Jefferson Medical College Hospital, Philadelphia, and at the Temple University School of Medicine, Philadelphia. He was chief at the Gastroenterologic Clinic, Lebanon Hospital, and Consulting Gastroenterological Clinic, Lebanon Hospital, and Consulting Gastroenterologist, Nassau County Sanitarium at Farmingdale.

He was a diplomate of the American Board of Internal Medicine and was a member of the American Medical Association, New York County Medical Society, New York State Medical Association, New York Academy of Medicine and others. He had been a Fellow of the American College of Physicians since 1926.

His confreres note with regret the passing of Dr. Kohn.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor, Eastern Division
New York

DR. WILLIAM JOHNSTON MALLORY

Dr. William Johnston Mallory, F.A.C.P., Lovettsville, Va., was born in Goochland, Va., in 1874. He attended Virginia Mechanics Institute; M.D., 1903, Columbian University (now George Washington University); M.A., 1914, George Washington University; postgraduate study in London, Cambridge and Berlin; Intern at the Civil Hospital, Manila, P. I., and also Attending Physician at the Civil Sanitarium, Baguio, P. I.; in 1910 became Instructor in Medicine at George Washington University and successively rose to Professor of Medicine by 1924, also to Chief of the Medical Service at George Washington University Hospital (Emeritus Professor of Medicine since 1940); for many years, Consultant in Gastroenterology, U. S. Veterans Administration; Veteran of World War I; member and past President, Washington Social Hygiene Society; member and former Secretary, American Gastroenterology Association; member, American Medical Association; member, Metropolitan and Cosmos Clubs; Diplomate, American Board of Internal Medicine; Charter Member of the American College of Physicians (1916).

After a dedicated life of active clinical practice and teaching in Washington, D. C., where he was for a number of years a Professor of Medicine at George Washington University, he retired to inactive status to Lovettsville, Va., in 1948. He was beloved by patients and colleagues during his active professional years and will be missed by a host of friends and neighbors to which he had become so attached in his years of retirement.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

DR. SIDNEY H. MARGULIS

Dr. Sidney Herbert Margulis, B.S., M.D., (Associate), Buffalo, N. Y., was born in Brooklyn, N. Y., Nov. 5, 1911. He attended Canisius College and later the University of Buffalo School of Medicine where he received his medical degree in 1938. He was an intern and Assistant Resident in Medicine at the Buffalo General Hospital, and later an Assistant Resident at the Holmes Hospital in Cincinnati, and finally Senior Resident in Medicine at the Meyer Memorial Hospital in Buffalo. At the time of his death he was an Associate in Medicine at the University of Buffalo School of Medicine, an Assistant Attending Physician at the Millard Fillmore Hospital in Buffalo, and Assistant Attending Physician in Medicine and Chief of the Peripheral Vascular Clinic at the Edward J. Meyer Memorial Hospital. He served during World War II from 1942–44.

His organizations included the Buffalo Academy of Medicine, Erie County Medical Society, New York State Medical Society, American Medical Association, American Heart Association, and Diplomate, American Board of Internal Medicine. He was elected an Associate of the American College of Physicians in 1954.

His professional interests in internal medicine were concentrated in the cardiovascular field in which he was recognized especially for his management of peripheral vascular problems. He was a conscientious, sincere physician, respected by his colleagues and beloved by his patients. Dr. Margulis is survived by his widow, Mrs. Doris M. Margulis, 181 North Park Ave., Buffalo 16, N. Y. His premature death was caused by acute leukemia.

JOHN H. TALBOTT, M.D., F.A.C.P.,
Governor for Western New York

DR. GEORGE IRVING SWETLOW

Dr. George I. Swetlow, F.A.C.P., died on August 20, 1956, at Brooklyn, New York, of congestive heart failure.

Dr. Swetlow was born at Newark, New Jersey, November 8, 1898. He received his degree of Doctor of Medicine in 1920 at Long Island College Hospital.

He was an intern at Brooklyn Jewish Hospital; Resident Physician, Kingston Avenue Hospital; Resident in Tuberculosis, Montefiore Hospital for Chronic Diseases; Resident, Neurological Division, Montefiore Hospital for Chronic Diseases.

He was Professor of Medico-Legal Jurisprudence, Brooklyn Law School, for the past several years; Lecturer in Medico-Legal Jurisprudence, New York Society of Insurance; Consulting Neurologist, Cumberland Hospital; Member of the New York Bar; Assistant Neurologist, Caledonian Hospital; Member, Kings County Medical Society, Brooklyn Society of Internal Medicine; Fellow of the American College of Physicians since 1926. He is author of many published papers and of two books dealing with Medical Jurisprudence.

Dr. Swetlow is survived by his widow, Mrs. Evelynne A. Swetlow of 73 Willow Street, Brooklyn, New York. His confreres note with sincere regret the passing of Dr. Swetlow.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. GUY HANFORD TURRELL

Dr. Guy H. Turrell, F.A.C.P., Smithtown Branch, New York, died on October 7, 1956, of a cerebral hemorrhage.

Dr. Turrell was born in Norwalk, Connecticut, on July 24, 1872. He received his degree of Doctor of Medicine at Columbia University College of Physicians and Surgeons in 1896.

He did postgraduate work at New York University, New York Postgraduate Medical School and Long Island Hospital.

His hospital appointments were as follows: Resident at the Bronx Home for Incurables in 1897; on the staff of Central Islip State Hospital, and was Sanitary Officer of Smithtown, 1905–31. He practiced medicine for well over fifty years and retired in April 1954.

He was a Diplomate of the American Board of Internal Medicine. He was active in his County and State Medical Societies and civic associations, among which was the Smithtown Library Association of which he was a member of the Board of Trustees from the year it was founded, and President from 1947 to 1954. He served in World War I in the army, attaining the rank of Major, and was stationed at Mineola where he did experimental work on the effect of high altitude on the heart. He was past President of Suffolk County Medical Society; Associated Physicians of Long Island, New York State Sanitary Officers Association, Second District Branch of the State Medical Association and the Southside Clinical Society; Member, American Public Health Association, New York Academy of Medicine, Suffolk County Tuberculosis and Public Health Association, American Medical Association and others. He has been a Fellow of the American College of Physicians since 1931.

He is survived by his wife, Mrs. L. V. Turrell of Smithtown Branch, New York, one son and two daughters. His confreres express sincere regret and sympathy to his family.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. FRANCES RALSTON VANZANT

Dr. Frances Ralston Vanzant, of Houston, Texas, died on August 27, 1956. She had been ill for a number of years with hypertension and diabetes and died of a terminal septicemia.

Dr. Vanzant was born June 20, 1902, in Ferris, Texas. She attended the public schools of Houston and graduated from Rice Institute, A.B. in 1922. She received her degree of Doctor of Medicine in 1926, from the University of Texas Medical School. After an internship in the John Sealy Hospital, Galveston, she received a fellowship in the Mayo Foundation. She worked at the Mayo Clinic almost four years, largely in the field of gastroenterology and experimental physiology. During this time she published a number of original studies on subjects related to her specialty. In 1931 she received the M.S. (Med.) degree, University of Minnesota (Mayo Foundation). She next received a fellowship in the Josiah Macy, Jr., Foundation on the basis of her work in gastroenterology. She studied for two years and then became an Instructor in Medicine and an Assistant Director at the University Hospital, University of Minnesota, Minneapolis, a post which she held for almost three years.

In 1935 Dr. Vanzant returned to her home in Houston, Texas, where she began the private practice of gastroenterology. When the war broke out in Spain in 1937, Dr. Vanzant became the first person in Houston, and perhaps the only woman physician, to join the Medical Bureau to Aid Spanish Democracy. She traveled in Spain with a unit of physicians and nurses and did active work in the war area, directing a medical hospital.

Dr. Vanzant served as Secretary of the Harris County Medical Society in 1937. She was a member of the Texas Medical Association, Mayo Clinic Alumni Association, American Gastroenterological Association, Texas Society of Gastroenterologists and Proctologists. She was elected a Fellow of the American College of Physicians in 1940.

She is survived by two brothers, Dr. Thomas J. Vanzant, of Houston, Texas, and Commander Joseph C. Vanzant, United States Navy, Long Beach, California.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

ANTICIPATIONS OF APRIL IN BOSTON

(Thirty-eighth Annual Session, American College of Physicians)

We of the College of Physicians who live in the Boston area are pleased that the Annual Session is to be held in our midst during the week of April 8–12. We delight in the prospect of being your hosts. Our sincere desire is that each of you will be able to come and to join with us in the professional stimulation, the intellectual rewards, and the social pleasures anticipated for the Boston meeting.

Boston is a community of undefinable character. Many of its cultural, scientific and industrial products are sufficiently well known to justify omission of details at this point. But the reasons why Boston has a certain uniqueness cannot be so lightly dispensed with because no one can agree as to exactly what these reasons are. History, geography, idealism, imagination, individualism, determination, maturity, solidity, intellectualism, "horse-sense," inherited shrewdness, and breeding are among the attributes mentioned. Yet if these or any other attributes do exist they are characteristics molded through a community of ever changing personnel. The leading citizens of one generation deeply influence but do not solely generate the leading citizens of the next. This fact is illustrated by noting that among the 180 members (Associates and Fellows) of the College of Physicians now practicing in the Greater Boston community, approximately 73% were born outside this community and that approximately 48% were born outside of New England! These "outlanders," attracted to Boston for varied reasons, have become a vitalizing part of the community strength and greatness, and illustrate that, though the reasons why may be obscure, Boston continues to be magnetic and inspirational.

A review of the medical facilities of Greater Boston emphasizes the part played by its three medical schools, Harvard, Boston University and Tufts. These schools graduate 145, 70 and 111 doctors each spring, call upon a total teaching staff of 1,400, 496, and 801, respectively, with voting Faculties of 338, 172 and 205 at each school. These figures indicate that for each medical student in Greater Boston there are more than two instructors.

Many hospitals enrich the community. A number of these hospitals are active teaching units for one or more of the medical schools. Others maintain teaching affiliations of a lesser degree.

The facilities of the Boston City Hospital, whose overall total bed capacity is 2,600, are used by all three medical schools and consists of various units including the Boston (Tuberculosis) Sanatorium in Mattapan, Long Island (Chronic) Hospital on an outer island of Boston Harbor and the Thorndike Memorial Laboratory as well as the other major units of the Boston City Hospital at 818 Harrison Avenue.

The Beth Israel Hospital (376 beds) at 330 Brookline Avenue is used by both Harvard and Tufts for teaching purposes.

The Boston Veterans Administration Hospital (950 beds) at Heath Street in Jamaica Plain is used by Tufts and Boston University and the West Roxbury Veterans Administration Hospital (300 beds) on Route 1 to Providence is used by Harvard.

The New England Center Hospital (272 beds) on Bennet Street includes the Pratt Diagnostic Hospital, the Boston Dispensary and the Floating Hospital, and is a major teaching unit for Tufts.

The Massachusetts Memorial Hospitals (400 beds) which include the Evans and the Robinson Memorial Hospitals at 750 Harrison Avenue and the Haynes (Contagious) Memorial Hospital on Corey Hill, are the major teaching units for Boston University.



AIR VIEW OF BOSTON

1—Huntington Avenue; 2—Arrow to Mechanics' Hall (just off picture); 3—Boston Public Library; 4—Sheraton Plaza; 5—Copley Square; 6—Boylston Street; 7—Dartmouth Street; 8—Exeter Street; 9—Commonwealth Avenue; 10—Beacon Street; 11—Massachusetts General Hospital; 12—North Station; 13—State House; 14—Hotel Bellevue; 15—Parker House; 16—Tremont Street; 17—Boston Common; 18—Public Gardens; 19—Hotel Statler; 20—Ritz Carlton Hotel; 21—St. James Avenue; 22—Stuart Street; 23—Back Bay Station; 24—Trinity Station; 25—University Club; 26—New England Mutual Life; 27—John Hancock Building.

The Children's Medical Center at 300 Longwood Avenue consists of the Children's Hospital (250 beds), the Infants' Hospital (40 beds), the House of the Good Samaritan (64 beds devoted to rheumatic fever or sequelae) as well as a convalescent home in Wellesley Hills and a sanatorium in Sharon. These facilities are used by Harvard.

Additional major Harvard teaching hospitals are the Peter Bent Brigham Hospital (280 beds) at 721 Huntington Avenue; the Boston Lying-in Hospital (196 beds) at 221 Longwood Avenue; the New England Center for Mental Health (formerly called the Boston Psychopathic Hospital) with 125 beds at 74 Fenwood Road; the Massachusetts Eye and Ear Infirmary at 243 Charles Street; and the Massachusetts General Hospital (890 beds) on Fruit Street. This latter includes the Baker Memorial Hospital and the Phillips House as well as the Huntington Memorial, the Vincent Memorial, the Burnham Memorial and the Hall-Mercer Hospitals. The McLean Hospital (Mental) in suburban Waverly is also a part of the Massachusetts General Hospital.

Numerous other hospitals affiliated in lesser degree to Harvard include the New England Deaconess Hospital of 375 beds including the Palmer Memorial Hospital, the George F. Baker Clinic (used extensively by the Joslin Group) and Cancer Research Institute; the Free Hospital for Women (91 beds) in Brookline; the Mount Auburn Hospital in Cambridge; and the Middlesex County (Tuberculosis) Hospital in Waltham.

The Boston University School of Medicine also uses the teaching facilities of the Robert Breck Brigham Hospital, the Chelsea Naval Hospital, the Channing Home (Tuberculosis), the Boston State (Mental) Hospital, the Pondville (Cancer) Hospital in Walpole, the Union Hospital in Framingham, the Providence (R. I.) Veterans Administration Hospital and the Huggins Hospital in Wolfeboro, New Hampshire.

Some teaching for Tufts University School of Medicine is also done at the Boston State (Mental) Hospital, the Metropolitan (Mental) Hospital in Waltham, the Worcester State (Mental) Hospital in Worcester, the Veterans Administration Hospital (Mental) at Bedford, the Massachusetts Eye and Ear Infirmary, the Booth Memorial Hospital (Brookline), the Cambridge City Hospital, the Carney Hospital, the St. Elizabeth's Hospital (Brighton), the St. Margaret's Hospital (Dorchester), the Providence (R. I.) Lying-in Hospital, the Lemuel Shattuck Hospital for chronic disease patients, the Jewish Memorial Hospital, the Malden Hospital, the Holy Ghost Hospital (Cambridge), the Mount Auburn Hospital (Cambridge), the Charles V. Chapin Hospital (Malden) and the Cambridge (Tuberculosis) Sanatorium.

In addition to the teaching hospitals listed are many more urban and suburban institutions of high calibre. Among these are the New England Baptist Hospital used extensively by the Lahey Clinic Staff, the Faulkner Hospital in Jamaica Plain, The United States Marine Hospital in Brighton, the Murphy General Hospital of the United States Army in Waltham, the New England Hospital for Women and Children, the Newton-Wellesley Hospital, the Melrose Hospital, the New England Sanitarium and Hospital in Stoneham, the Symmes Arlington Hospital, the Brooks Hospital on the top of Corey Hill in Brookline, the Chelsea Memorial Hospital, the Emerson Hospital in Concord, the Whidden Memorial Hospital in Everett, the Lawrence Memorial Hospital in Medford, the Winchester Hospital, the Quincy City Hospital, the Milton Hospital and Convalescent Home, the Winthrop Community Hospital, the New England Peabody Home for Crippled Children in Newton, and numerous others.

Prominent medical institutions are not restricted to medical schools and hospitals. The important impact of the Lahey Clinic on the well-being of the community and on medical knowledge throughout the nation is well known. The Overholt Thoracic Clinic performs superlative service. The James Jackson Putnam Children's



AIR VIEW OF HARVARD MEDICAL SCHOOL AREA

1—Harvard Medical School; 2—Peter Bent Brigham Hospital; 3—Harvard School of Public Health; 4—Children's Hospital; 5—House of the Good Samaritan; 6—New England Center for Mental Health (formerly Boston Psychopathic Hospital); 7—New England Deaconess Hospital; 8—Beth Israel Hospital; 9—Vanderbilt Hall (dormitory for Harvard Medical School); 10—Boston Lying-in Hospital; 11—Simmons College; 12—Massachusetts College of Pharmacy; 13—Angel Memorial (Animal) Hospital; 14—Harvard Dental School.

Center serves a teaching outlet for Boston University School of Medicine as does the Judge Baker Guidance Center, which is an affiliate of the Children's Medical Center.

Besides the medical libraries connected with each of the various medical schools and many of the hospitals, Boston is fortunate to have one of the great medical libraries of the world, the Boston Medical Library at 8 The Fenway. A medical museum of considerable professional and historical interest, the Warren Anatomical Museum, is located in the administration building of the Harvard Medical School.

Boston has no "Harley Street" but there are areas of the community to which doctors not officed in or near a hospital or medical school are particularly attracted. Along and adjoining Commonwealth Avenue and Beacon Street from Berkeley out to and just beyond Kenmore Square, with particular concentration at Kenmore Square and in the blocks on either side of Massachusetts Avenue, there are many medical offices. Again on Beacon Street as it has stretched into the town of Brookline, particularly in the 1100's and 1200's, there is a further concentration of offices. In the business and "down town" area of Boston, there is the same marked scarcity of doctors' offices as in many other large cities.

Boston has a number of industries closely connected with the medical world. The Sanborn Company in Cambridge, makers of electrocardiographs and metabolism testers; Warren E. Collins, Inc., makers of scientific instruments; the Grass Instrument Company in Quincy, makers of electroencephalographs; the MacGregor Instrument Company in Needham; Baird Associates, Inc. in Cambridge, who are absorbing the Atomic Instrument Company; the Tracerlab Inc.; the Jarrell-Ash Company; the Macalaster Bicknell Company in Cambridge; Codman and Shurtleff, Inc.; the Randall Faichney Corp.; the Fenwal Laboratories, Inc. in Framingham; the International Equipment Company; the Linde Air Products Company, are among the nationally known plants.

The headquarters of such pharmaceutical houses as Otis Clapp & Son and Davies Rose & Company are in Boston; that of E. L. Patch & Company is in nearby Stoneham. The Tailby Nason Company is in Cambridge and the Gray Pharmaceutical Company is in Needham. In nearby Worcester are both Brewer & Company and Buffington's.

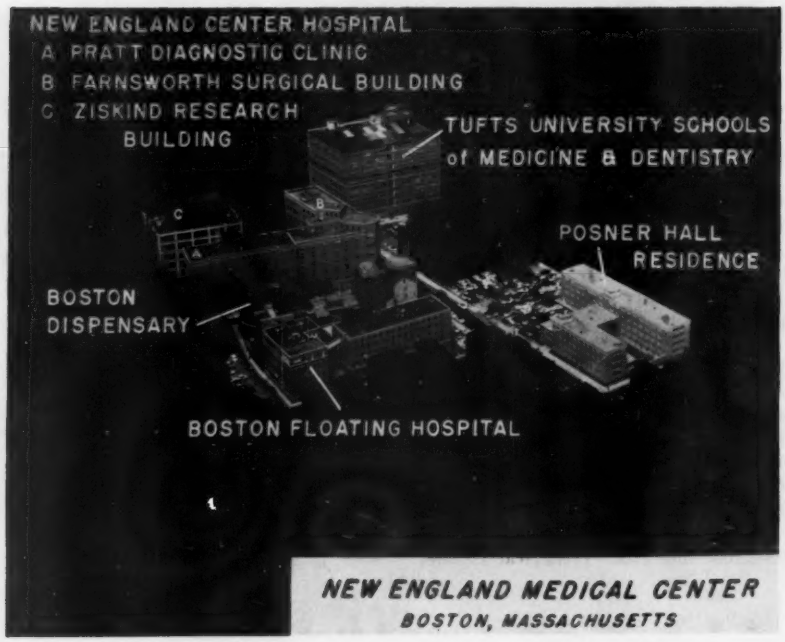
Four nationally known life insurance companies originate in Boston: the New England Life, the John Hancock, the Columbian National, and the Boston Life. Hospitalization, casualty and health insurance are also products of the Boston Home Offices of the Liberty Mutual, the American Mutual Liability, the Factory Mutual, and the Massachusetts Bonding and Insurance Companies.

In non-medical fields, the most unique character of Boston's activities or industries, besides the rapidly expanding and highly technical electronic field, is that of Education. Besides Harvard University and Radcliffe College, the Massachusetts Institute of Technology, Wellesley College, Tufts University, Simmons College, Boston University, Boston College, Northeastern University, the New England Conservatory of Music, Wheaton College (at Norton), Brandeis University (at Waltham), the Babson Institute of Business Administration (at Wellesley Hills), the Museum School of the Boston Museum of Fine Arts, Wheelock College, Pine Manor (at Wellesley), Longy School of Music, Emerson College, Emmanuel College, Lasell Junior College, and the Perkins School for the Blind (at Watertown), there are many additional excellent and famous smaller colleges and graduate or specialty schools providing splendid educational facilities in professional, artistic, musical, technical, secretarial, home making and varied other fields. Furthermore, in secondary education, the high concentration of leading college preparatory schools in or readily available to Massachusetts is well known.

But, there is much that is exciting in Boston beyond serious professional and intellectual interests. Historical Greater Boston is well documented in pamphlets,



The Medical School of Boston University, Massachusetts Memorial Hospitals.



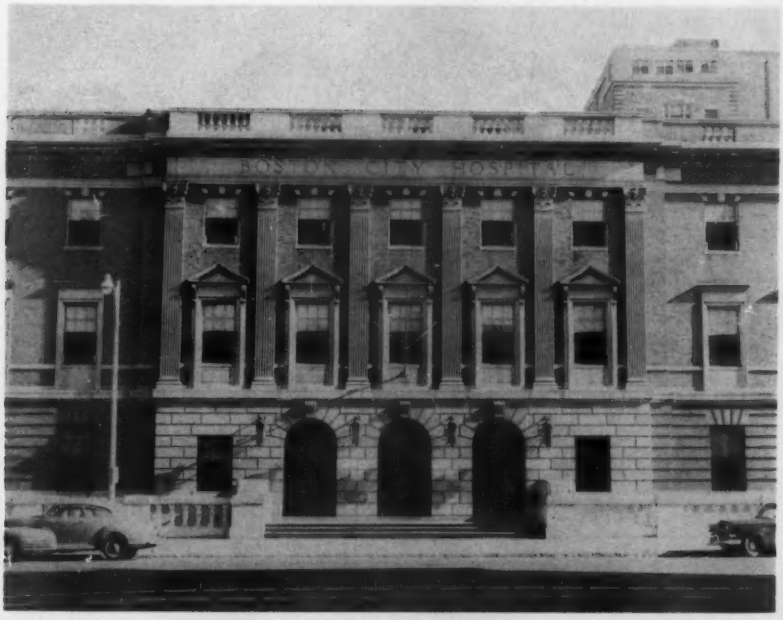


Massachusetts General Hospital, George Robert White Building, Bulfinch Building

guide books, and through planned tours readily available after arrival in the city. Considerable time visiting historical places can be spent not only on foot or by bus or auto in and around Boston itself but in the whole New England area.

Although Boston has been known in the theatrical world as the musical comedy town, our middle-aged pleasures may prefer us to learn that Boston is reputed as having the best quality of meat in the United States! The story goes that because Boston is a seafood town, only the best meat is sent here to compete! We trust you will find this pragmatically correct when you test any of the many restaurants at the time of your impending visit.

Not only professionally, intellectually, educationally, aspirationally and gastronomically may Boston appeal but also Greater Boston has much delight aimed to the pleasures of children. Those of us who are still children at heart will enjoy the Museum of Science from push button electronic models or playing with a delightful pet porcupine to viewing the astral wonders of the Planetarium; the ancient Automobile Museum on the Lars Anderson Estate in Brookline (including a limousine with a "Head"); the Nautical Museum at M.I.T. (especially for Kansas whale and shark experts); the geographical inspiration of the Babson World Globe Building in Wellesley and the Christian Science Publishing Company's "Mapparium" behind the Mother Church near Mechanics' Building; the views from the Tower of the John Hancock Building; the Children's Museum at 60 Burroughs Street in Jamaica Plain; the Zoo at Franklin Park (City) and Stoneham (Metropolitan District Commission); the Railway and Locomotive Historical Society in the Baker Library of the Harvard Business School (opposite the Harvard Stadium) or/and the Sloan Automotive Museum showing historic aircraft and automatic power plants at M.I.T.



Entrance, Boston City Hospital



Capitol of the Commonwealth of Massachusetts, Overlooking Boston Common

BUT, what about the weather? The unusual is classical. In early April, one does not expect but must still be prepared for raw, cold disagreeable weather though a snow blizzard is most unlikely. Spring is just around the corner. Prima vera is in the making. Do not be deceived but be prepared! Warm buildings, good taxis, and short distances minimize the inconveniences of unsettled weather. Dress accordingly.

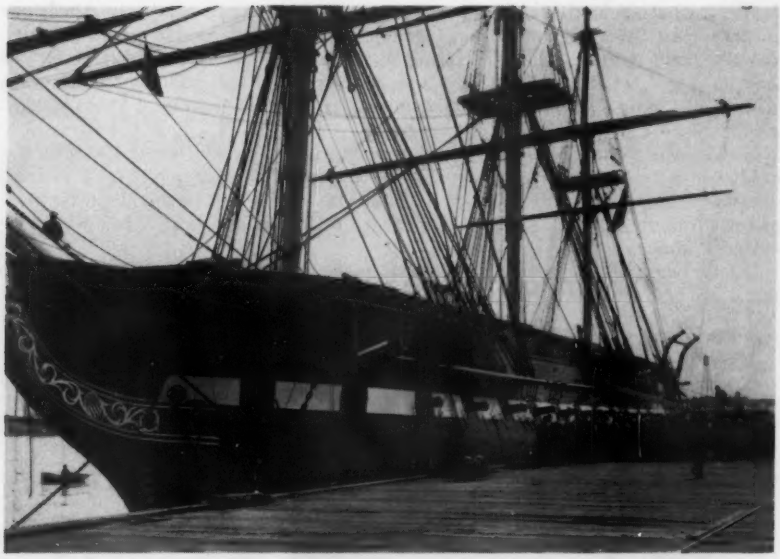
If extensive sightseeing is planned throughout New England before and after the meeting, do not forget that the season is early. And for those athletically inclined do not forget that some of the best skiing of the season may still be found during early April north of Boston, though perhaps only at the dangerous Tuckerman's Ravine in the White Mountains of New Hampshire.

To all our guests, the Greater Boston component of the College of Physicians sends a warm and cheerful welcome! We look forward to your visit.

MILTON HENRY CLIFFORD



Statue of Paul Revere, with the Old North Church in the Background



Old Ironsides at Dock in Boston Harbor

TENTATIVE PROGRAM
THE AMERICAN COLLEGE OF PHYSICIANS

Thirty-Eighth Annual Session

BOSTON, MASSACHUSETTS

April 8–12, 1957

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GENERAL INFORMATION

Mechanics' Building—Many are the fond and some are the pained memories that the mention of this famous old exposition hall stirs in the minds of all who have visited or helped to organize meetings, conventions, shows of one or another sort, or even Annual Sessions within its four walls. However, let it be known that here is a building of seventy-five years, still sturdy, with floors a little less creaky than in 1950 due to reflooring, and still one of the most adaptable meeting places for a gathering such as ours that exists.

The Exhibition Hall, which will house our 146 technical exhibits, leads into the Grand Hall with a capacity of about 4,500. Here will be held the General Sessions, the Morning Lectures and the Clinical Physiological, Biochemical and Pathological Conferences.

Above the Exhibition Hall are rooms for smaller meetings: Paul Revere Hall, capacity 480; Talbot Hall, capacity 400; and the Paul Revere Banquet Hall, capacity 250. In these rooms the colored televised clinics will be viewed and panels and the afternoon symposia will be held. A smaller room, the Paul Revere Reception Room, in back of the larger Paul Revere Hall, will house an exhibit of the audio-visual demonstration and explanation of auscultatory findings in various valvular defects. On this same floor restaurant facilities will be available.

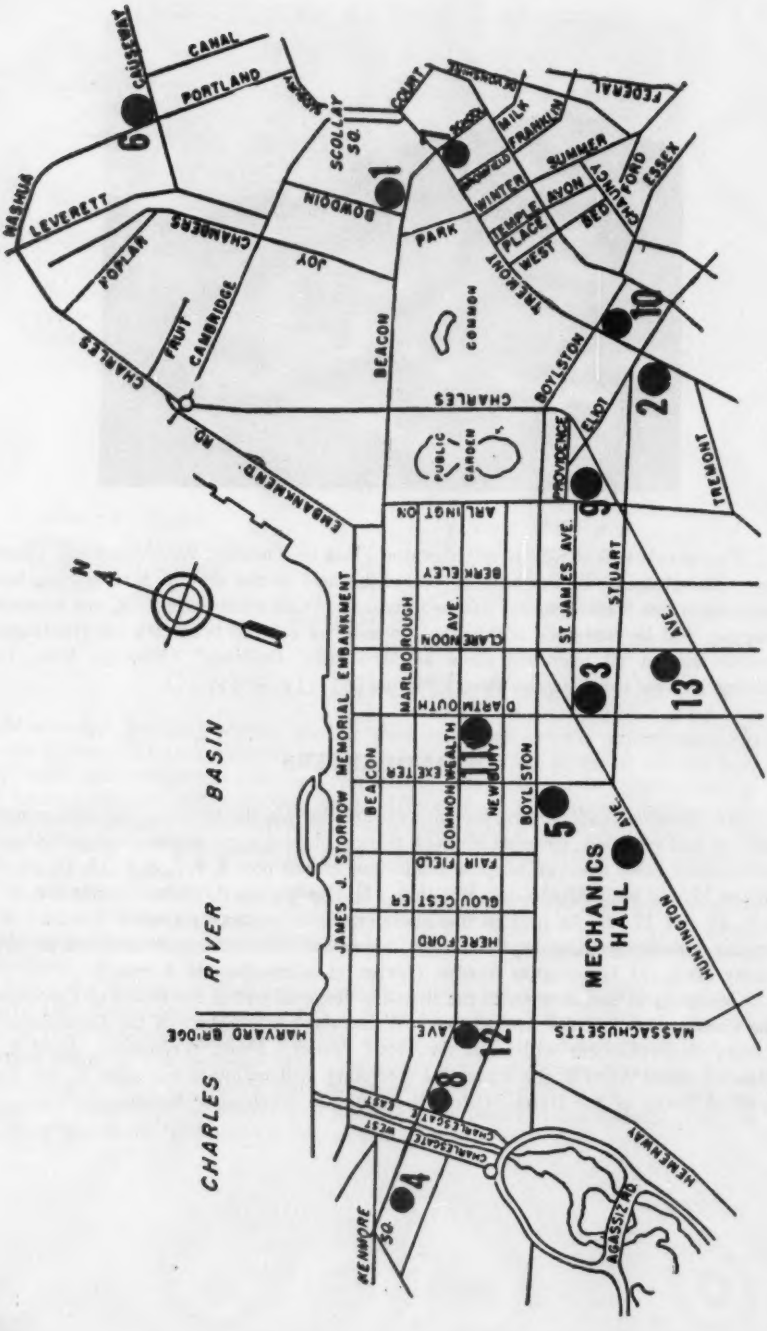


Two panels will be held in the Sheraton Plaza on Tuesday, Wednesday and Thursday. The Hospital Clinics will, of course, be held in the several participating hospitals for which transportation will be provided. With these exceptions, our scientific program will be contained within that "wonderful old red brick ark on Huntington Avenue known all over the place as Mechanics' Building" (Rudolph Elie, The Roving Eye published in the Boston *Herald*).

HEADQUARTERS

Registration headquarters, the Information Bureau, the technical exhibits, general sessions and symposia, morning lectures, clinical physiological-biochemical-pathological conferences, color televised hospital clinics and panels nos. 3, 4, 7, 8, 9, 12, 13, 14, 15, 16 and 17 will be in Mechanics' Building, 111 Huntington Avenue. Panels nos. 1, 2, 5, 6, 10 and 11 will be held in the Sheraton Plaza in nearby Copley Square. The concert Monday evening by the Boston Symphony Orchestra will be given at Symphony Hall, 251 Huntington Avenue (corner of Massachusetts Avenue).

Meetings of Committees, of the Board of Regents and of the Board of Governors, the Convocation and the Annual Banquet and the headquarters of the Committee on Ladies' Entertainment will be at the Hotel Statler. From Wednesday, April 3, to Monday noon, April 8, the Executive Secretary will maintain his office in the Connecticut Room of the Hotel Statler; thereafter in Mechanics' Building.


CANAL
PORTLAND
CAUSEWAY
SCOLLAY SQ.
COURT
SCHOOL
MILK
FRANKLIN
FEDERAL
SUMMER
WINTER
AVON
BEDFORD
CHAUNCY
ESSEX
TEMPLE PLACE
WEST
TREMONT
BOWDOIN
PARK
JOY
CHAMBERS
LEVERETT
MARSHALL
POPLAR
FRUIT
CAMBRIDGE
CHARLES
BEACON
COMMON
PUBLIC GARDEN
BOYLSTON
ELIOT
PROVIDENCE
EMBANKMENT RD
ARLINGTON
BERKELEY
CLARENDON AVE.
MARLBOROUGH
DARTMOUTH
EXETER
BEACON
COMMONWEALTH
NEWBURY
BOYLSTON
FAIRFIELD
GLOUCESTER
HEREFORD
ST JAMES AVE.
STUART
AVE.
HUNTINGTON AVE.
MECHANICS HALL
JAMES J. STORROW MEMORIAL EMBANKMENT
CHARLES RIVER BASIN
HARVARD BRIDGE
MASSACHUSETTS AVE
CHARLESGATE EAST
CHARLESGATE WEST
MEMORIAL DR
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HOTEL ACCOMMODATIONS

The Statler and Sheraton Plaza Hotels will be official hotel headquarters, but all of the following hotels will be official hotels for the convention. An A.C.P. Housing Bureau, conducted under the Boston Convention Bureau, 80 Federal St., Boston 10, Mass., will handle all hotel reservations, except that the Executive Secretary will provide hotel reservations at the Statler Hotel for Officers, Regents, Governors and Speakers on the program. Members and guests-at-large may utilize the official reservation form accompanying the formal program. Additional copies of the hotel reservation form may be obtained from the College Headquarters, 4200 Pine St., Philadelphia 4, Pa.

LIST OF HOTELS

Map No.	Hotel	For One Person	For Two Persons		Suites
			Double Bed	Twin Beds	
	Beaconsfield	$5.75–$11.00	$ 8.75–$11.85	$ 8.75–$14.50	$10.00–$24.50
1	Bellevue	6.00– 9.00	9.00– 12.00	11.00– 18.00	25.00
2	Bradford	7.00– 10.50	10.00– 12.00	11.50– 15.00	16.00– 20.00
	Braemore	7.00– 10.00	11.00– 12.00	11.00– 13.00	15.00– 24.00
	Commander	6.00– 9.00	10.00– 13.00	12.00– 13.00	18.00– 30.00
	Continental	5.00– 9.00	9.00– 11.00	11.00– 13.00	18.00 and up
	Copley Square	4.00– 6.50	6.00– 8.00	7.00– 9.00	12.00– 16.00§
	Essex	4.00– 6.50	6.50– 10.50	7.50– 10.50	
12	Harvard Club	7.00		13.00	
4	Kenmore	6.85– 11.00	11.00– 15.00	11.00– 15.00	17.00– 24.00
5	Lenox	5.00– 7.00	8.00– 9.00	8.00– 12.00	10.00– 14.00
	Lincolnshire	6.50– 11.00	11.00– 13.00	11.00– 13.00	13.00– 26.00
6	Manger	6.00– 7.50	8.50– 10.00	9.50– 11.00	
7	Parker House	7.00– 9.50	11.00– 13.00	13.00– 16.00	23.00– 25.00
3	*Sheraton Plaza	6.85– 13.00	11.00– 16.00	11.50– 17.00	25.00– 39.00
	Sherry Biltmore	5.50– 9.00	8.50– 12.00	10.00– 16.00	15.00– 20.00
8	Somerset	7.00– 11.00	11.00	12.00– 16.00	18.00– 42.00
9	*Statler	7.00– 11.00	10.50– 14.50	11.50– 16.00	30.50 and up
10	Touraine	6.00– 8.00	9.50– 12.00	9.50– 12.00	18.00
	1200 Beacon St. Motel	9.00		13.00	
13	University Club	7.00	9.00	10.00	
11	Vendome	5.00– 8.00	7.00– 10.00	8.00– 12.00	12.00– 16.00

* Headquarter's Hotels. § Three to Four Persons.

Who May Register—

(*a*) All members of the American College of Physicians in good standing for 1957.

(*b*) All newly elected members.

(*c*) Graduate medical students pursuing courses in local institutions of Boston, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions**; admission to exhibits, general sessions, morning lectures, symposia, CPC's, Hospital Clinics, and TV programs.

(*d*) Members of the staff, including interns, of the Boston Hospitals participating in the program, without registration fee, **upon presentation of proper identification**; admission to exhibits, general sessions, morning lectures,

symposia, CPC's, Hospital Clinics and TV programs (this does not include courtesy staff members).

(*e*) Bona fide hospital residents, regardless of their location in North America, without registration fee, **upon presentation of proper credentials from their hospitals**; admission to exhibits, general sessions, morning lectures, symposia, CPC's, Hospital Clinics and TV programs.

(*f*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States, Canada or Mexico, without registration fee, **upon presentation of proper credentials.**

(*g*) Qualified physicians, who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published, starting with the July number) included within such fee.

(*h*) Full-time medical teachers holding the rank of Assistant Professor or lower, **upon presentation of proper credentials from their medical schools,** shall be entitled to a reduction in the registration fee to $12.50.

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 8, advance registration of members and exhibitors will be provided for by mail. The Registration Bureau will be set up for advance registration in the Mechanics' Building on Sunday, April 7, from 2:30 P.M. to 5:00 P.M. The Registration Bureau will be open throughout the week from 8:45 A.M. to 5:30 P.M.

Advance Registration of Members—In order to facilitate quick registration at the meeting for members of the College, an advance registration form, with directions, will be enclosed with the formal Program to all Fellows and Associates. The success and justification of the plan is wholly dependent upon the co-operation of members, and thus the directions should be carefully noted and the proper forms returned to the Executive Offices of the College long in advance, so that each member's envelope of forms and badge will be ready for him when he calls at the Advance Registration Window. The use of this form will eliminate long lines and delays so frequently encountered at large conventions. A member, however, should not send in this form unless he is sure he is going to be present. Last year there was a 10% "no show" of advance registrations, resulting in waste of time and material.

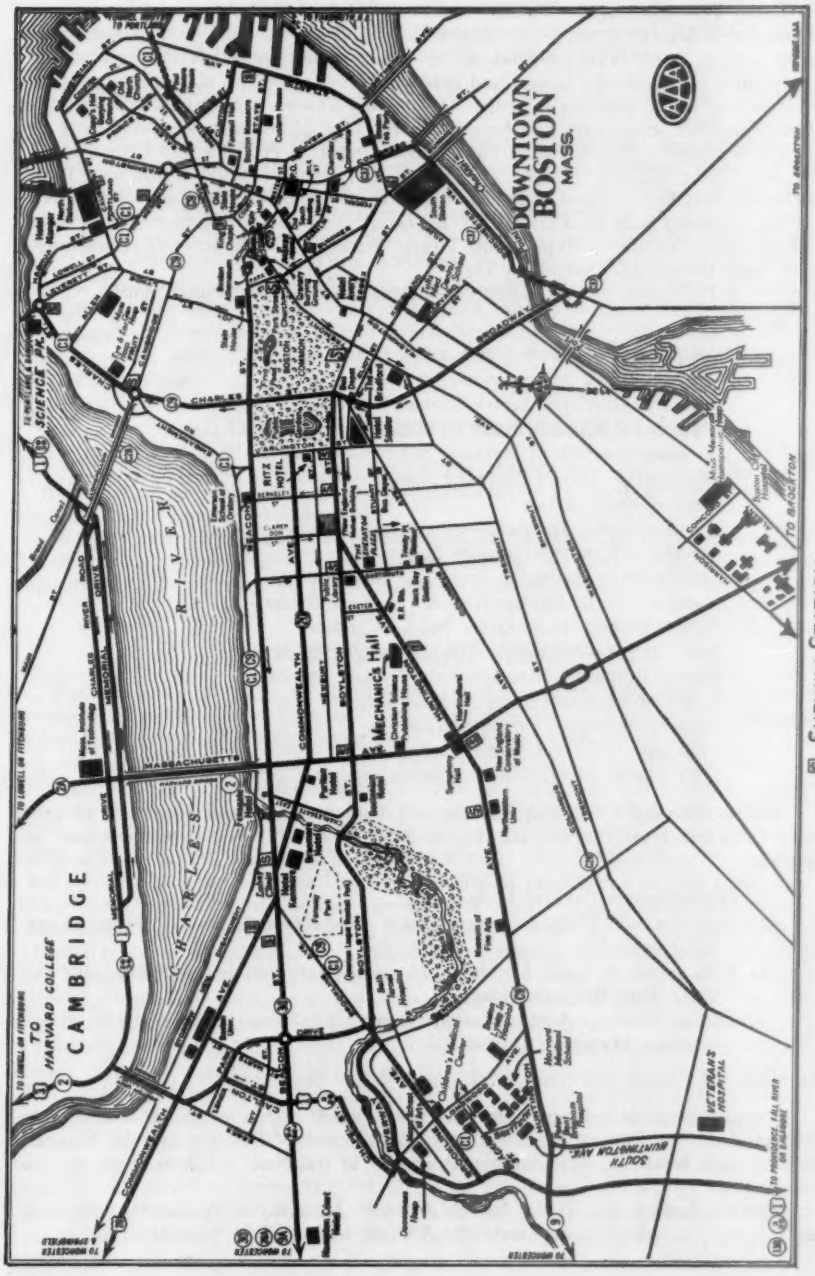
Registration Blanks for Panel Discussions will be enclosed with the final program to members of the College. Non-members will secure registration blanks at the Registration Bureau during the Session.

Daily Bulletins—A Daily Bulletin of registrations will be published at this meeting.

Information and Message Center—A special window at the general Registration Bureau will handle all messages, incoming telegrams and incoming mail.

Bulletin Board for special announcements will be located near the Registration Bureau.

First Aid Room—A First Aid room with a nurse in attendance will be established on the main floor of Mechanics' Building.


DOWNTOWN BOSTON MASS.
CAMBRIDGE
TO HARVARD COLLEGE
CHARLES RIVER
BOSTON
Mechanics Hall
VETERAN'S HOSPITAL
SOUTH HUNTINGTON AVE.
SUBWAY STATION

Local Transportation—Distances between Mechanics' Building and the various Boston hotels are not great. An effort will be made to have the various taxi companies provide ample taxis available at the various hotels and other strategic points.

In most instances, the easiest and most inexpensive method of getting from the hotels to Mechanics' Building is by the Metropolitan Transit Authority which operates subways, surface street cars and buses. There is an MTA entrance point close to nearly every hotel. The Sheraton Plaza, Copley Square, Vendome and Lenox hotels and the Copley Subway Station are only a few minutes walking distance from Mechanics' Building. There is a subway station at Mechanics' Building where three carlines, outbound from the Park Street, Boylston Street and Arlington Street subway stations stop: Arborway-Huntington, Heath Street and Northeastern University. These same cars stop at Symphony Hall.

The MTA points nearest hotels other than those in the Copley Square region are as follows:

Beaconsfield—Beacon Street surface car
Bellevue—Park Street Subway Station
Bradford—Boylston Street Subway Station
Braemore—Kenmore Subway Station
Commander—Bus to Harvard Square—subway to Park Street
Continental—Bus to Harvard Square—subway to Park Street
Essex—South Station
Harvard Club—Massachusetts Avenue Station
Kenmore—Kenmore Subway Station
Lincolnshire—Arlington Street Subway Station
Manger—North Station Elevated to Park Street
Parker House—Park Street Subway Station
Ritz Carlton—Arlington Street Subway Station
Sherry Biltmore—Massachusetts Avenue Station
Somerset—Massachusetts Avenue Station
Statler—Arlington Street Station
Touraine—Boylston Street Station
1200 Beacon Street—Beacon Street Surface Car

For the Hospital Clinics on Tuesday and Thursday mornings, buses will be provided from the Hotel Statler, starting at 8:30 A.M. The bus routes will run as follows:

(1) Massachusetts General Hospital
(2) New England Medical Center, Boston City Hospital, Massachusetts Memorial Hospitals
(3) Beth Israel Hospital, Children's Hospital, Harvard Medical School and the Peter Bent Brigham Hospital
(4) Boston Veterans Administration Hospital (Tuesday) and the Robert Breck Brigham Hospital (Thursday)

At 11:00 A.M. buses will return to Mechanics' Building.

Tuesday evening between 5:30 and 7:00 o'clock a shuttle system will operate between the Hotel Statler, the Sheraton Plaza, Mechanics' Building and the Museum of Fine Arts for those attending the Reception to the New Members given by the Governors.

For the Ladies' Tea at the Isabella Gardner Museum on Wednesday afternoon and for the Thursday trip to Sturbridge Village, buses will be provided.

Tickets for local bus transportation will be available at the Registration Desk in Mechanics' Building and at the Ladies' Headquarters in the Hotel Statler. Tickets for the Sturbridge Village trip will be sold at the Ladies' Headquarters only.

Parking—There will be ample parking space in the rear of Mechanics' Building at $1.00 per day.

The Annual Business Meeting of the College will be held at 2:00 P.M. on Thursday, April 11, immediately preceding the afternoon General Session. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors and the annual reports of the Secretary-General, Executive Secretary and Treasurer. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award, the Willard O. Thompson Memorial Traveling Scholarship Award and the Mead Johnson Graduate Scholarship Awards. The President-Elect, Dr. Richard A. Kern, Philadelphia, Pa., will be inducted into office. Be present and know your College!

BOARD AND COMMITTEE MEETINGS

All meetings will be held at the Hotel Statler at times and places to be indicated. A full schedule of such meetings will be published in the final program. Special meetings will be announced and posted.

A Reception and Dinner for the members of the Board of Regents, Board of Governors, Committee Chairmen, distinguished guests, and their wives, will be held Sunday, April 7, at 7:00 P.M. in the Ballroom Assembly of the Hotel Statler.

SPECIAL FEATURES

Post-Convention Tour to the Caribbean—Immediately following the Boston Session, a Post-Convention Tour will be conducted to Puerto Rico, St. Thomas, the Dominican Republic and Haiti. The group will leave Boston by special planes via Pan American Airlines, Saturday, April 13, arriving in San Juan, Puerto Rico, that afternoon. There will be a Reception at the San Juan Airport, after which the party will transfer to the La Rada Hotel. A Presidential Cocktail Party will follow in the evening. On Sunday, April 14, members of the group will visit El Yunque National Rain Forest and Luquillo Beach. Monday, April 15, will be devoted to a more formal program with the large membership of the College in San Juan, consisting of an inspection tour of the University of Puerto Rico School of Medicine, a Scientific Program at the Medical School building, luncheon at the San Patricio Veterans Hospital as guests of the Puerto Rico members of the College, followed by a Scientific Meeting there, and a Reception and Dinner in the evening at the University Club in conjunction with the San Juan members of the College. In this program, Dr. Rafael Rodriguez-Molina, College Governor for Puerto Rico; Dr. E. Harold Hinman, F.A.C.P., Dean, Professor and Head of the Department of Microbiology of the University of Puerto Rico; Dr. Ramon Suarez, Sr., former A.C.P. Governor and former Vice President of the College; and Dr. Guillermo Pico, President of the Medical Society of Puerto Rico, will cooperate both socially and scientifically. On Tuesday, April 16, the group will fly to St. Thomas for sightseeing, shopping and luncheon. On April 17 the group flies to Ciudad Trujillo, Dominican Republic, and transfers to the Hotel Embajador. This requires only a very short flight. The afternoon will be utilized for visiting the San Domingo Medical College, the first medical school in the New World, and two or three of the new and very

modern hospitals, such as the Children's Hospital and the General Hospital. On Thursday, April 18, the group will drive to Boca Chica for luncheon and the Isle of Matica. On Friday, April 19, in the morning, the group will make the short flight to Port-au-Prince, Haiti, and will stay at the Hotel Riviera. There will be an opportunity for sightseeing including Kenscoff Mountain; a Reception and Cocktail Party will be held in the evening. On Saturday, April 20, the group will be taken by motor coach to visit the famous Albert Schweitzer Memorial Hospital at Saint Marc, a two and a half hour ride to the north of Port-au-Prince in the Artibonite Valley. This is a small general hospital of seventy-five beds, operated by five American physicians and one Haitian dentist. Dr. Larimer Mellon heads the group. It is a small modern hospital set down in a rural tropical community and has received wide publicity in American magazines.

The party will return to Port-au-Prince in the middle of the afternoon and those returning to New York by ship will embark on the *S.S. Cristobal* in the evening. arriving at New York, Wednesday, April 24. Those desiring to return by air to Miami or New York will leave on Sunday, April 21. For full and detailed information contact the Tour Conductor, Mr. Joseph P. Sims, Jr., The House of Travel, 1600 Walnut Street, Philadelphia 3, Pennsylvania. It is important that each member anticipating making the trip conclude his arrangements with the least possible delay. Family and friends are cordially invited to accompany the group.

Symphony Concert, Boston Symphony Orchestra, Dr. Charles Munch, Conducting, Monday, April 8, 8:30 P.M.—The College is again privileged to attend a concert by the Boston Symphony Orchestra under the leadership of its distinguished conductor, Dr. Charles Munch. Through the good offices of Dr. Roger I. Lee it was our good fortune to be entertained by this world famed Orchestra in 1941 and in 1950. Our members who attended those concerts will remember with a true sense of thrill their beauty which has charmed and held the inspired loyalty of Symphony goers throughout the years and will appreciate the reasons for the Orchestra's outstanding triumphs on its recent tour of Europe.

The generosity of the Wyeth Laboratories has made it possible for us to look forward to this evening of exceptional pleasure.

Tickets will be for admission only with the exception of a reserved section for Officers, Regents, distinguished guests, committee members and their ladies. Due to the limited capacity of Symphony Hall, which can seat 2,631 persons, tickets will be limited to not more than four per member prior to 3:30 P.M. of the day of the Concert. There will be no advance applications and tickets may be obtained at the time of registration or until 5:00 P.M., Monday, April 8.

Reception and Cocktails, tendered by the Governors of the College to new Associates and Direct Fellows: the Boston Museum of Fine Arts, Tuesday, April 9, 5:30 to 7:30 P.M.—The Governors of the College extend an invitation to all new Associates and Direct Fellows, and their wives, who were elected on April 14 and November 10, 1956, to attend a Reception and Cocktail Party at the Boston Museum of Fine Arts, Tuesday, from 5:30 to 7:30 P.M. We are fortunate in obtaining the privilege of holding this gathering in the Rotunda and in the room where the Great Tapestries are hung. The occasion will provide opportunities for the new members and their wives to meet the Officers and Regents of the College and their wives as well as to mingle with one another. Following the Reception, those who so desire may go through the Museum.

Special invitations will be sent out by the Governors and it is urged that acceptances or declinations be returned promptly to enable adequate planning and transportation.

The Annual Convocation, the President's Reception and Dance: Hotel Statler, Wednesday evening, April 10, 8:40 P.M.—The 1957 Annual Convocation of the College will take place in the Ballroom of the Hotel Statler at the time above designated. All members of the College and their families, and the public who are interested, are cordially invited to witness the impressive academic procession and other ceremonies. Tickets will not be required. All physicians elected Fellows of the College since the 1956 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors, distinguished guests on the program, new Fellows to be inducted, candidates for Honorary Fellowships and Masterships, Latin-American Fellows, Traveling Scholars and Research Fellows of the College are requested to assemble in the Georgian Room and adjacent parlors for gowning at 7:00 P.M. The Pre-Convocation Assembly will be formed and the Procession will move promptly at 8:40 o'clock.

The Convocation Ceremony will include the induction of new Fellows and an address by the President of the College, Dr. Walter L. Palmer. The John Phillips Memorial Medal for 1957, the James D. Bruce Memorial Medal for 1957 and the Alfred Stengel Diploma for 1957 will be awarded. Masterships will be conferred on three distinguished Fellows of the College and two Honorary Fellowships will be conferred on two distinguished foreign guests. There will be present officers or representatives of The American College of Surgeons, The American Medical Association, The Royal College of Physicians and Surgeons of Canada, The Royal College of Physicians of London, and The Royal Australasian College of Physicians.

Immediately following the Convocation, the President's Reception will be held in the Ballroom Assembly, immediately adjacent to the Ballroom. Dancing will start in the Ballroom about 10:30 P.M., continuing to 1:00 A.M. The music will be furnished by Ruby Newman's Orchestra. Tables for individual parties will be available around the periphery of the dance floor and in the Ballroom Assembly.

The Annual Banquet: Imperial Ballroom, Hotel Statler, Thursday evening, April 11, 8:00 P.M.—At 7:00 P.M. in the Georgian Room there will be a "Dutch Treat" Cocktail Party to which all members and their guests are invited.

The Banquet will be held in the Imperial Ballroom at 8:00 P.M. The local Committee in cooperation with the cuisine of the Hotel are selecting a menu to tickle the taste-buds of the members, be they from Puerto Rico or Quebec, Panama or British Columbia—intervening states included.

Ruby Newman will furnish the music. One Doctor Howard B. Sprague, F.A.C.P., raconteur par excellence and M.C. sine qua non, will be Toastmaster. Professor Allan R. Foley of Dartmouth College will regale us with a bit of Vermont lore which, in its wit and humor, is as fresh as a breeze from the Northland in springtime.

Tickets for the Banquet will be assigned by tables and those wishing to sit together must apply together or on a single application. It is important that reservations be made early. Tickets may be purchased at the Registration Desk, Mechanics' Building, up to 3:00 P.M., Wednesday, April 10, when it will be necessary to close the sale to enable adequate planning by the Committee. The price per ticket will be $8.50.

ENTERTAINMENT OF VISITING LADIES

The Committee on Entertainment of Visiting Ladies has planned a program aimed to provide activities that will abound in interest as well as sociability. The Ladies' Headquarters in the Maine and New Hampshire Rooms of the Hotel Statler offer a central meeting place and it is hoped that the Visiting Ladies will avail themselves of it to renew old acquaintances and make new ones at the Morning Coffee Hours as well as during the varied planned events.

Of particular interest will be the trip to Old Sturbridge Village—some sixty miles from Boston where New England life of 150 years ago has been recaptured, not alone by the 18th century houses and furnishings, but by craftsmen and women actually plying their crafts and daily duties with the tools, equipment and methods of those early days.

It is also the particular pleasure of the Ladies' Committee to receive the visiting ladies for tea at the famous and beautiful Isabella Gardner Museum in The Fenway. The Fashion Show, the many available trips to famous houses and points of historical and aesthetic interest, as well as participation in the social events of the Men's program, offer a spectrum of activities which, it is hoped, will bring enjoyment to the visiting ladies. In this hope a cordial welcome is extended.

Certain of the entertainment features are limited in accommodations; certain of them require advance guarantees. For these reasons, early return of reservation cards and early registration upon arrival in Boston is earnestly requested.

The Information Desk

Lists of resturants, shops, beauty parlors and theatres are available.

Places of Interest

Arnold Arboretum
Athenaeum
Boston Public Library—murals
The Old State House
Museum at the Massachusetts Institute of Technology
Mapparium, Christian Science Publishing House
Museum of Fine Arts
Museum of Science
Agassiz Museum (Harvard)
Isabella Stewart Gardner Museum
William Hayes Fogg Art Museum (Harvard)
Peabody Museum of Archaeology and Ethnology (Harvard)

Transportation

Buses will leave the Columbus Avenue entrance to the Hotel Statler for all trips.

LADIES' PROGRAM

Sunday, April 7, 2:00 to 5:00 P.M.

Registration in the Maine Room, Hotel Statler.

Monday, April 8, "Open House," 9:00 A.M. to 5:00 P.M.

The Ladies' Committee and the wives of the Governors and Regents of the College will receive members during the registration hours. Coffee will be served. This occasion will give us great pleasure to meet you personally and for you to meet each other.

10:00 A.M. to 12:00 M.

Mrs. Palmer cordially invites the wives of the newly elected members to meet her in the New Hampshire Room.

Evening—8:30

Concert by the Boston Symphony Orchestra for the College, Dr. Charles Munch, Conductor. Symphony Hall. Tickets obtainable at Registration Desk, Mechanics' Building.

Tuesday, April 9, 9:00 A.M. to 5:00 P.M.

Registration in the Maine Room of the Hotel Statler. Coffee will be served.

Afternoon—12:30

Luncheon and Fashion Show, Imperial Ballroom, Hotel Statler. Spring and Summer Fashions by Hurwitch Brothers, of Boston. Tickets, $6.50, tax included.

Evening—5:30 to 7:30

Cocktail party for newly-elected members and their wives, who, as guests of the Governors, are invited to meet the Officers of the College, at the Boston Museum of Fine Arts. Buses will shuttle between the Hotel Statler, the Sheraton Plaza, Mechanics' Building and the Art Museum. Round trip tickets available at the Registration Desk, 75¢.

Wednesday, April 10, 9:00 A.M. to 5:00 P.M.

Registration and Coffee, Maine Room, Hotel Statler.

11:00 A.M. to 4:00 P.M.

Tour of private art collections in prominent Boston homes and studios. Tickets, $10.00. Limited number available.

Afternoon—4:00 to 6:00

Reception and Tea. Isabella Stewart Gardner Museum, 280 The Fenway. The ladies will be the guests of the Ladies' Committee. Admission by ticket. Buses will leave the Hotel Statler at 3:30. Fare—round trip, 75¢.

Evening—8:30

Convocation in the Imperial Ballroom of the Hotel Statler, followed by the President's Reception and Dance. Music by Ruby Newman.

Thursday, April 11, 9:00 A.M. to 5:00 P.M.

Registration, New Hampshire Room, Hotel Statler.

9:30 A.M. to 4:30 P.M.

Trip to Old Sturbridge Village, a renovated New England village of the early eighteen hundreds. See craftsmen at work on pottery, metal-working and weaving. Choice collections of antiques, furniture, clocks, china, glass and pewter. Tickets, $5.00; admission and bus fare included. Lunches may be purchased at the Tavern.

10:00 A.M.

Optional trip of historic and modern Boston. Time, 2½ hours. Tickets, $2.00.

Evening

7:00 Dutch Treat cocktails, Georgian Room—Hotel Statler.

8:00 Annual Banquet, Imperial Ballroom.
Toastmaster—Dr. Howard B. Sprague.
Speaker—Professor Allan R. Foley, "Tales from the Vermont Hills."

Medical Teaching Films—Several new medical films will be shown at the Medical Film Guild's headquarters, booths 220–222, in the technical exhibit area. Of special mention are the following two films: (1) "Peripheral Vascular Diseases—Physiology and Efficacy of a New Therapeutic Agent," prepared with the collaboration of several medical colleges and institutions; (2) "The Blood Vessel and Living Pathology," prepared under the direction of Professors Brenton R. Lutz and George P. Fulton of Boston University Graduate School.

SUPPLEMENTARY GROUP MEETINGS

Commission on Professional and Hospital Activities has scheduled a luncheon at the Hotel Statler, Bay State Room, Monday, April 8 at 12:00 noon. Invited are all members of the Commission and medical staff members of hospitals participating in the professional activity study who are in attendance at the Boston Session of the College. Doctor Vergil N. Slee, in charge.

Cleveland Clinic Foundation invites all former fellows of the Cleveland Clinic, and their wives, to a reception and cocktail party on Tuesday, April 9, 5:30 P.M., Hotel

Statler. Doctor Charles L. Leedham, in charge. Consult bulletin board for location of room.

American Society of Hematology, Doctor James L. Tullis, Temporary Chairman, will hold a scientific session on Sunday, April 7, 1957, 2:00–5:30 P.M., at the Harvard Club. In addition to the charter members, consisting of current members of the International Society of Hematology, the invitation is extended to all members of the American College of Physicians who are interested.

American Society of Internal Medicine, Doctor Claude P. Callaway, Secretary-Treasurer; Doctor Lewis T. Bullock, Chairman—will hold a meeting of its representatives on Sunday, April 7, 1957, 10:00 A.M., at the Statler Hotel. Consult bulletin board for location of room.

Governors' Receptions and Cocktail Parties—Several Governors are planning receptions and cocktail parties for members from their particular states or territories sometime during the week. Watch for announcements on the bulletin board at the Hotel Statler or at Mechanics' Building.

The Technical Exhibit will be located on the main floor of the historical Mechanics' Building. More than 100 firms have subscribed for booths. Their exhibits will cover the wide range of interest of internists and allied specialists everywhere, and will serve as an outstanding example of the ever-improving technical exhibits of the College.

The Committee on Exhibits maintains high standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation. Irrelevant exhibits are eliminated, and only firms which present a group of approved products or services of scientific interest and real worth may exhibit.

Exhibits will be open from 8:45 A.M. to 5:30 P.M. daily, Monday through Thursday, and from 8:45 A.M. to 2:15 P.M. on Friday. The Technical Exhibitors gauge the meeting by the amount of interest shown and the co-operation displayed by members of the College. The exhibits constitute a real educational program in connection with the Annual Session, and members and guests are encouraged to accord the exhibitors courteous and interested attention.

PARTIAL LIST OF TECHNICAL EXHIBITORS

	Booth
Abbott Laboratories, North Chicago, Ill.	424–426
Adolph's Ltd., Los Angeles, Calif.	504
American Cyanamid Company, Fine Chemical Division, New York, N. Y.	231–233
American Ferment Co., Inc., New York, N. Y.	402
Ames Company, Inc., Elkhart, Ind.	318
Appleton-Century-Crofts, Inc., New York, N. Y.	234
Association of American University Presses, New Haven, Conn.	207
Audio-Digest Foundation, Glendale, Calif.	101
Ayerst Laboratories, New York, N. Y.	415–417
W. A. Baum Co., Inc., Copiague, L. I., N. Y.	511
Becton, Dickinson and Company, Rutherford, N. J.	428
V. Ray Bennett & Associates, Inc., Los Angeles, Calif.	608
Bilhuber-Knoll Corp., Orange, N. J.	335
Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y.	616
Bowen & Company, Inc., Bethesda, Md.	110
Brewer & Company, Inc., Worcester, Mass.	308
Burdick Corporation, The, Milton, Wis.	516
Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, N. Y.	432
Burton, Parsons & Company, Washington, D. C.	332

	Booth
Cambridge Instrument Co., Inc., New York, N. Y.	219
Carnation Company, Los Angeles, Calif.	502
Ciba Pharmaceutical Products, Inc., Summit, N. J.	302–304–505–507
Warren E. Collins, Inc., Boston, Mass.	331
Davies, Rose & Company, Limited, Boston, Mass.	232
F. A. Davis Company, Philadelphia, Pa.	224
Desitin Chemical Company, Providence, R. I.	410
Devereux Schools, Devon, Pa.	102
DeVilbiss Company, The, Somerset, Pa.	404
Doho Chemical Corporation, New York, N. Y.	221–223
Eaton Laboratories, Norwich, N. Y.	228–230
J. H. Emerson Company, Cambridge, Mass.	311
C. B. Fleet Company, Inc., Lynchburg, Va.	330
E. Fougera & Company, Inc., New York, N. Y.	416
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, New York, N. Y.	414
General Foods Corporation, White Plains, N. Y.	403–405–513–515–610–612
Gerber Products Company, Fremont, Mich.	211
Gray Pharmaceutical Company, Inc., Newton, Mass.	200–201
Grune & Stratton, Inc., New York, N. Y.	320–322
H. J. Heinz Company, Pittsburgh, Pa.	314
Paul B. Hoeber, Inc., Medical Books Department of Harper & Brothers, New York, N. Y.	100
Hoffman-La Roche, Inc., Nutley, N. J.	517
Hollister-Stier Laboratories, Philadelphia, Pa.	104
Irwin, Neisler & Company, Decatur, Ill.	326
Ives-Cameron Company, Philadelphia, Pa.	412
Jones Metabolism Equipment Company, Chicago, Ill.	204
LaMotte Chemical Products Company, The, Chestertown, Md.	411
Lea & Febiger, Philadelphia, Pa.	229
Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.	235
Eli Lilly and Company, Indianapolis, Ind.	313–315–317
J. B. Lippincott Company, Philadelphia, Pa.	423
Little, Brown & Company, Boston, Mass.	334
Lloyd Brothers, Inc., Cincinnati, Ohio	316
Macmillan Company, The, New York, N. Y.	300
Massachusetts Indemnity & Life Insurance Co., Boston, Mass.	425
S. E. Massengill Company, The, Bristol, Tenn.	324
McNeil Laboratories, Inc., Philadelphia, Pa.	107
MD Publications, Inc., New York, N. Y.	431
Mead Johnson & Company, Evansville, Ind.	202
Medco Products Company, Philadelphia, Pa.	109
Medical Bureau, The, Chicago, Ill.	111

	Booth
Medical Film Guild, Ltd., New York, N. Y.	220–222
Medical Protective Company, The, Fort Wayne, Ind.	407
Merck Sharp & Dohme, Division of Merck & Company, Inc., Philadelphia, Pa.	303–305–307
Wm. S. Merrell Company, The, Cincinnati, Ohio	323–325
Miles Reproducer Company, New York, N. Y.	512
C. V. Mosby Company, The, St. Louis, Mo.	503
National Drug Company, The, Philadelphia, Pa.	510
Nepera Chemical Co., Inc., Yonkers, N. Y.	418
New England Journal of Medicine, The, Boston, Mass.	514
Nordmark Pharmaceutical Laboratories, Inc., Irvington, N. J.	509
Ortho Pharmaceutical Corporation, Raritan, N. J.	409
Parke, Davis & Company, Detroit, Mich.	400
Pet Milk Company, St. Louis, Mo.	225
Pfizer Laboratories, Brooklyn, N. Y.	500–501
Pharmacia Laboratories, Inc., Rochester, Minn.	106
Postgraduate Medicine, Minneapolis, Minn.	108
Purdue Frederick Company, The, New York, N. Y.	518
Riker Laboratories, Inc., Los Angeles, Calif.	327–329
Ritter Company, Inc., Rochester, N. Y.	614
A. H. Robins Company, Inc., Richmond, Va.	213
J. B. Roerig and Company, Chicago, Ill.	209
William H. Rorer, Inc., Philadelphia, Pa.	508
Sanborn Company, Cambridge, Mass.	419–421
Sandoz Pharmaceuticals, Hanover, N. J.	328
W. B. Saunders Company, Philadelphia, Pa.	103–105
Schenley Laboratories, Inc., New York, N. Y.	609
Schering Corporation, Bloomfield, N. J.	429
G. D. Searle & Co., Chicago, Ill.	430
Smith, Kline & French Laboratories, Philadelphia, Pa.	306–333
E. R. Squibb & Sons, New York, N. Y.	203–205
Stuart Company, The, Chicago, Ill.	519
Taylor Instrument Companies, Rochester, N. Y.	613–615
U. S. Vitamin Corporation, New York, N. Y.	226
Upjohn Company, The, Kalamazoo, Mich.	215–217
Wallace Laboratories, New Brunswick, N. Y.	206–208
Henry K. Wampole & Co., Inc., Philadelphia, Pa.	309
Warner-Chilcott Laboratories, Morris Plains, N. J.	210
White Laboratories, Inc., Kenilworth, N. J.	427
William & Wilkins Co., The, Baltimore, Md.	310
Winthrop Laboratories, Inc., New York, N. Y.	420–422
Woodward Medical Personnel Bureau, Chicago, Ill.	312
Wyeth Laboratories, Philadelphia, Pa.	319–321
Year Book Publishers, Inc., The, Chicago, Ill.	413
Yorke Publishing Company, Inc., The, New York, N. Y.	506

SPECIAL SCIENTIFIC EXHIBIT

Paul Revere Reception Room
Mechanics' Building

Title—**Audio-Visual Demonstration of the Value of Haemodynamic Phenomena in Certain Aspects of Cardiac Diagnosis**

(New York University Post-Graduate Medical School)

Participants—J. Scott Butterworth, F.A.C.P.
Maurice R. Chassin, F.A.C.P.
Robert McGrath, F.A.C.P.
Edmund H. Reppert, Jr. (by invitation).
John J. Thorpe (Associate).

In this exhibit tape recordings of heart sounds and murmurs will be used to demonstrate the physics of sound and the mechanisms of cardiac murmurs and sounds. The auscultatory findings in various forms of heart disease will be reproduced. Illustrative electrocardiograms, slides of the x-ray configuration of the heart and catheterization data pertinent to the material being demonstrated will also be presented and coordinated. The time schedule for the specific demonstrations will be posted at the entrance to the Demonstration Room. The following is a list of the subject material:

1. Physics of Sound. (Approximately 30 minutes.)
2. Normal and Abnormal Sounds, with attention to Splitting of the Second Pulmonic Sound, Pulmonary and Aortic Snaps and Systolic Clicks. (Approximately 30 minutes.)
3. Mitral Stenosis. Variations in the Auscultatory Findings in Regular Rhythm and Auricular Fibrillation. The Delay of the First Sound and Changes in the Timing of the Opening Snap in Relation to the Degree of Stenosis. Evaluation of Apical/Systolic Murmurs Associated with Mitral Stenosis. (Approximately 45 minutes.)
4. Aortic Valvular Lesions. (Approximately 45 minutes.)
5. Certain Aspects of Congenital Heart Disease, with particular reference to the Importance of the Second Pulmonic Sound in Diagnosis. (Approximately 45 minutes.)

OUTLINE OF THE BOSTON SESSION

(Sessions will be held chiefly in Mechanics' Building, other than Hospital Clinics)

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
9:00 A.M. to 11:00 A.M.	Reserved for Registration and INSPECTION OF EXHIBITS	Hospital Clinics Color TV	Morning Lectures Color TV	Hospital Clinics Color TV	Morning Lectures Color TV
11:00 A.M. to 11:40 A.M.		Intermission	Intermission	Intermission	Intermission
11:40 A.M. to 1:00 P.M.		Panels (4)	Panels (5)	Panels (5)	Panels (3)
11:40 A.M. to 1:00 P.M.		CPC's	CPC's	CPC's	CPC's
2:00 P.M. to 3:10 P.M.	1st General Session	2nd General Session	3rd General Session	Annual Business Meeting 4th General Session	5th General Session 3:45 Adjournment (Technical Exhibit closed at 2:15 P.M.)
3:10 P.M. to 3:45 P.M.	Intermission	Intermission	Intermission	Intermission	
3:45 P.M. to 5:00 P.M.	1st General Session (Continued) — Symposia (2)	2nd General Session (Continued) — Symposia (2)	3rd General Session (Continued) — Symposia (2)	4th General Session (Continued) — Symposia (2)	
Evening	8:30 P.M. Symphony Concert Symphony Hall	5:30–7:30 P.M. Governor's Reception to new members and wives Museum of Fine Arts	8:40 P.M. Convocation and President's Reception	7:00 P.M. "Dutch Treat" Cocktails 8:00 P.M. Banquet	

GENERAL SESSIONS PROGRAM

Grand Hall, Mechanics' Building

FIRST GENERAL SESSION

Monday Afternoon, April 8, 1957

Presiding Officer

Richard P. Stetson, F.A.C.P., Boston

General Chairman

P.M.

2:00 **Addresses of Welcome:**

His Excellency, FOSTER FURCOLO
Governor of the Commonwealth of Massachusetts

The Honorable JOHN B. HYNES
Mayor of the City of Boston.

HOWARD F. ROOT, F.A.C.P.
President of the Massachusetts Medical Society.

JOSEPH M. HAYMAN, JR., F.A.C.P.
Dean of Tufts University School of Medicine, on behalf of the three medical schools of Boston.

Response to Addresses of Welcome.

WALTER L. PALMER, F.A.C.P., Chicago
President, The American College of Physicians.

Presiding Officer

Walter L. Palmer, F.A.C.P., President

2:30 **The John Phillips Memorial Lecture: Some Challenging Aspects of Hemoglobin Metabolism.**

CECIL J. WATSON, F.A.C.P., Minneapolis, Minn.
Professor of Medicine, University of Minnesota Medical School.

2:50 **The Lilly Lecture: Critical Review of Some Antidiabetic Compounds.**

HANS HEINRICH BERG, M.D., (by invitation), Hamburg, Germany.
Professor of Internal Medicine, University of Hamburg.

3:10 INTERMISSION.

Presiding Officer

Chester M. Jones, F.A.C.P., Boston, Mass.
First Vice President, A.C.P.

(*Note there are two concurrent Symposia at this time*)

3:45 **The Value of Continuous (1 to 10 Years) Long Term Anticoagulant Therapy.**

BENJAMIN MANCHESTER, F.A.C.P., Washington, D. C.
Assistant Clinical Professor of Medicine, George Washington University School of Medicine.

4:00 **Limited Use of Anticoagulants in Acute Myocardial Infarction: Analysis of 1,000 "Good Risk" Cases.**

HENRY I. RUSSEK, F.A.C.P., Staten Island, N. Y.
Consultant in Cardiovascular Research, U. S. Public Health Service Hospital.

BURTON L. ZOHMAN, F.A.C.P., Brooklyn, N. Y.
Associate Clinical Professor of Medicine, State University of New York College of Medicine at New York City.

4:15 **The Varied Clinical Manifestations of Pulmonary Embolism.**
HAROLD L. ISRAEL, F.A.C.P., Philadelphia, Pa.
Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine; Chief, Department of Medicine, Philadelphia General Hospital.
FRANZ GOLDSTEIN, M.D., (by invitation), Philadelphia, Pa.
Senior Resident Physician in Medicine, Graduate Hospital of the University of Pennsylvania.

4:30 **Cerebral Vascular Insufficiency: An Experimental and Clinical Explanation of the Transient Stroke.**
ELIOT CORDAY, F.A.C.P., Los Angeles, Calif.
Clinical Professor of Medicine, University of California School of Medicine at Los Angeles.
SANFORD ROTHENBERG, M.D., (by invitation), Los Angeles, Calif.
Associate Attending Surgeon, Neurosurgery Clinic, Cedars of Lebanon Hospital.

4:45 **The Medical Aspects of Motor Vehicle Accident Prevention.**
HAROLD BRANDALEONE, F.A.C.P., New York, N. Y.
Assistant Clinical Professor of Medicine, New York University College of Medicine.
GERALD J. FRIEDMAN, F.A.C.P., New York, N. Y.
Instructor, Department of Physical Medicine and Rehabilitation, New York University College of Medicine.

5:00 ADJOURNMENT.

5:05 **Elective: The Blood Vessel and Living Pathology.**
A motion picture film in color and sound—18 minutes. Directed by Dr. George P. Fulton and Dr. Brenton R. Lutz, Department of Biology, Graduate School of Boston University. The film vividly portrays the circulating blood from the normal to complete stasis and covers vasomotor activity, morphological elements, modification in behavior, platelet thrombo-embolism, control of bleeding, ionizing radiation and tumor growth. Produced by Medical Film Guild, Ltd., through a grant for Postgraduate Education by U. S. Vitamin Corporation.

SECOND GENERAL SESSION

Grand Hall, Mechanics' Building

Tuesday Afternoon, April 9, 1957

Presiding Officer

Richard A. Kern, F.A.C.P., Philadelphia, Pa.
President-Elect, A.C.P.

P.M.
2:00 **The James D. Bruce Memorial Lecture on Preventive Medicine: Some Basic, Unsolved Problems in the Prevention of Rheumatic Fever.**
ALVIN F. COBURN, M.D., D.Sc., (by invitation), Chappaqua, N. Y.

2:20 **Post-diphtheritic Myocarditis.**
EDWARD G. SAYERS, M.D., F.R.A.C.P., F.R.C.P. (Lond.), (by invitation), Auckland, New Zealand.
President, The Royal Australasian College of Physicians; Senior Visiting Physician, Auckland, New Zealand; Sub-dean, Auckland Branch of the Faculty of Medicine, University of Otago.

2:40 **Respiratory Viruses and Heart Disease.**
EARL N. SILBER, (Associate), Chicago, Ill.
Assistant Clinical Professor of Medicine, Chicago Medical School; Adjunct Attending Physician, Department of Medicine, and Assistant Director of Medical Education, Michael Reese Hospital.

2:55 **Pulmonary Hypertensive Cardiovascular Disease.**
THOMAS W. MATTINGLY, Colonel (MC), U.S.A., F.A.C.P., Washington, D. C.
Chief, Cardiology Service, Walter Reed Hospital; Clinical Assistant Professor of Medicine, Georgetown University School of Medicine.
LOREN F. PARMLEY, Lieutenant Colonel, (MC), U.S.A., (Associate), Washington, D. C.
Walter Reed Army Hospital.
ROBERT J. HALL, Major, (MC), U.S.A., (Associate), Washington, D. C.
Walter Reed Army Hospital.

3:10 INTERMISSION.

Presiding Officer

George H. Anderson, F.A.C.P., Spokane, Wash.
Second Vice President, A.C.P.

(*Note there are two concurrent Symposia at this time*)

3:45 **Visualization of Intracardiac Structures with Gaseous Carbon Dioxide.**
THOMAS M. DURANT, F.A.C.P., Philadelphia, Pa.
Professor and Head of the Department of Medicine, Temple University School of Medicine.

4:00 **Atrial Septal Defects in Patients Past Middle Age.**
HAROLD A. LYONS, F.A.C.P., Brooklyn, N. Y.
Associate Professor of Medicine and Director of Cardiopulmonary Laboratory, State University of New York College of Medicine at New York City.

4:15 **Disability Two to Five Years After Mitral Commissurotomy; An Evaluation by Clinical Criteria and Exercise Tolerance.**
GORDON A. LOGAN, M.D., (by invitation), Seattle, Wash.
Clinical Associate in Medicine, University of Washington School of Medicine.
ROBERT A. BRUCE, F.A.C.P., Seattle, Wash.
Associate Professor of Medicine, University of Washington School of Medicine.
GORDON G. BERGY, M.D., (by invitation), Seattle, Wash.
University of Washington School of Medicine.
K. ALVIN MERENDINO, M.D., (by invitation), Seattle, Wash.
Professor of Surgery, University of Washington School of Medicine.

4:30 **Diagnostic Features of Myxoma of the Auricle, A Surgically Curable Lesion.**
JOHN COLLINS HARVEY, (Associate), Baltimore, Md.
Assistant Professor of Medicine, Johns Hopkins University School of Medicine.

4:45 **To Be or Not to Be a Gallop.**
JAMES V. WARREN, F.A.C.P., Durham, N. C.
Professor of Medicine, Duke University School of Medicine.

5:00 ADJOURNMENT.

5:05 **Elective: Peripheral Vascular Disease—Physiology and Efficacy of a New Therapeutic Agent.**
A motion picture film in color and sound—35 minutes. Collaborating institutions include: Vascular Clinic, St. Vincent's Hospital, New York; Department of Physical Medicine, Montefiore Hospital, New York; Bird S. Coler Hospital Division, New York Medical College; Department of Biology, Graduate School of Boston University; Commonwealth of Massachusetts' Lemuel Shattuck Hospital, Jamaica Plain. The film depicts hazards in neglecting the many circulatory involvements which are classified from intermittent claudication to phlebothrombosis. Effect of spasm superimposed on circulatory obstruction is shown. The physiologic rationale in skin vs. muscle blood flow is presented. Effects of vasodilators are studied pharmacologically and clinically on hundreds of patients. From the "Medical Film of the Month" series produced by Medical Film Guild, Ltd.

THIRD GENERAL SESSION

Grand Hall, Mechanics' Building

Wednesday Afternoon, April 10, 1957

Presiding Officer

T. Grier Miller, F.A.C.P., Philadelphia, Pa.
Past President, Past Regent, Past Marshal, A.C.P.

P.M.

2:00 **The James D. Bruce Memorial Lecture on Preventive Medicine: Characteristics of the Individual as Guideposts to the Prevention of Heart Disease.**
CAROLINE BEDELL THOMAS, F.A.C.P., Baltimore, Md.
Associate Professor of Medicine, Johns Hopkins University School of Medicine.

2:20 **Observations on Carotenaemia.**
THE RIGHT HONORABLE THE LORD COHEN OF BIRKENHEAD, M.D., D.Sc., LL.D., F.R.C.P., F.F.R., F.S.A., J.P., (by invitation), Liverpool, England.
Professor of Medicine, Liverpool University.

2:40 **Staphylococci: On the Ubiquitous Nature of Human Infections and Their Control by Antimicrobial Agents Singly or in Combination.**
PAUL A. BUNN, F.A.C.P., Syracuse, N. Y.
Professor of Medicine and Director, Infectious Disease and Tuberculosis Laboratories, State University of New York College of Medicine at Syracuse.
A. L. BALTCH, M.D., (by invitation), Syracuse, N. Y.
MISS W. OSBORNE, (by invitation), Syracuse, N. Y.
L. CANARILI, B.S., (by invitation), Syracuse, N. Y.
State University of New York College of Medicine at Syracuse.

2:55 Rheumatoid Aortitis: An Unusual Manifestation of Rheumatoid Disease.

WILLIAM S. CLARK, M.D., (Associate), Cleveland, Ohio.
Associate Professor of Medicine, Western Reserve University School of Medicine.

WALTER BAUER, F.A.C.P., Boston, Mass.
Jackson Professor of Clinical Medicine, Harvard Medical School.

J. PETER KULKA, M.D., (by invitation), Boston, Mass.
Associate in Pathology at the Peter Bent Brigham Hospital.

3:10 INTERMISSION.

Presiding Officer

Truman G. Schnabel, Sr., F.A.C.P., Philadelphia, Pa.

Third Vice President, A.C.P.

(*Note there are two concurrent Symposia at this time*)

3:45 Chronic Sodium Chloride Toxicity: Prolonged Survival of Rats Eating Added Potassium Chloride.

GEORGE R. MENEELY, F.A.C.P., Nashville, Tenn.
Associate Professor of Medicine, Vanderbilt University School of Medicine; Director, Research Laboratory and Radioisotope Unit, Veterans Administration Hospital.

4:00 Pitfalls in the Diagnosis of Pheochromocytoma.

JAMES A. EVANS, F.A.C.P., Boston, Mass.
Senior Physician, Lahey Clinic.

4:15 The Diagnostic Approach to Hypertension Due to Unilateral Kidney Disease.

EUGENE B. FERRIS, F.A.C.P., New York, N. Y.
Regent, A.C.P.; Medical Director, American Heart Association.

ALBERT A. BRUST, (Associate), Emory University, Ga.
Associate Professor of Internal Medicine, Emory University School of Medicine.

4:30 The Identification and Clinical Significance of Casts.

GEORGE E. SCHREINER, (Associate), Washington, D. C.
Assistant Professor of Medicine, Director of the Renal Clinic, Georgetown University Medical Center.

4:45 The Effect of Antecedent Diet on Urine Concentrating Ability.

WILLIAM H. MERONEY, Lieutenant Colonel, (MC), USA, (Associate), Washington, D. C.
Chief, Department of Metabolism, Walter Reed Army Institute of Research.

MILTON E. RUBINI, M.D., (by invitation), Washington, D. C.

WILLIAM B. BLYTHE, M.D., (by invitation), Washington, D. C.
Walter Reed Army Institute of Research.

5:00 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 10, 1957

8:40 o'Clock

Imperial Ballroom, Hotel Statler

Lemuel C. McGee, Marshal
Marshall N. Fulton, Assistant Marshal

Fellows to be inducted, Officers, Regents, Governors, Distinguished Guests, and Recipients of Awards; Gowning 7:00 P.M., Georgian Room and adjacent parlors, mezzanine floor; Pre-Convocation Assembly, 7:45 P.M., Georgian Room, mezzanine floor.

All members of the profession and the general public are cordially invited.

1. Processional.
2. **The President's Address: "Tradition and Progress in Medicine." Walter L. Palmer.**
3. Conferring of Fellowships by the President.
4. Conferring of Masterships by the President.
5. Conferring of Honorary Fellowships by the President.
6. A Presentation to the Royal College of Physicians of London.
   GEORGE F. STRONG.
   Acceptance by:
   THE RIGHT HONORABLE THE LORD COHEN OF BIRKENHEAD.
7. Presentation of the James D. Bruce Memorial Medal for 1957.
8. Presentation of the John Phillips Memorial Medal for 1957.
9. Presentation of the Alfred Stengel Memorial Award for 1957.
10. Recessional.

The President's Reception will follow in the Ballroom Assembly at 10:30 o'clock. The audience is requested to vacate the Ballroom temporarily while the room is reset for Dancing. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Grand Hall, Mechanics' Building

Thursday Afternoon, April 11, 1957

Presiding Officer

Walter L. Palmer, F.A.C.P., President

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award, the Willard O. Thompson Memorial Traveling Scholarship Award and the Mead Johnson Postgraduate Residency Scholarship Awards. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; an amendment to the Constitution and

By-Laws will be presented; elections of new Officers, Regents and Governors will take place; President-Elect Richard A. Kern, of Philadelphia, Pa., will be inducted as President and will make a brief inaugural address.

Presiding Officer

Richard A. Kern, F.A.C.P., President

2:45 The Function of the Joint Commission on Accreditation of Hospitals.
LeRoy H. Sloan, F.A.C.P., Chicago, Ill.
Past President, A.C.P.; A.C.P. Commissioner and Chairman, Board of Commissioners, Joint Commission on Accreditation of Hospitals; Clinical Professor of Medicine, University of Illinois College of Medicine.

3:00 The Significance of Human Illness Due to Strain 19 Brucella Abortus.
Wesley W. Spink, F.A.C.P., Minneapolis, Minn.
Governor, A.C.P.; Professor of Medicine, University of Minnesota Medical School.

3:15 INTERMISSION.

Presiding Officer

George F. Strong, F.A.C.P., Vancouver, B. C.
Past President and Regent, A.C.P.

(*Note there are two concurrent Symposia at this time*)

3:45 Treatment of Acute Porphyria with Chelating Agents.
Henry A. Peters, (Associate), Madison, Wis.
Assistant Professor of Neuropsychiatry, Department of Neurology, University of Wisconsin Medical School.

4:00 An Evaluation of Dietary Protein in the Treatment of Acute and Chronic Liver Disease.
Thomas C. Chalmers, (Associate), Jamaica Plain, Mass.
Clinical Associate in Medicine, Harvard Medical School; Chief of Medical Services, Lemuel Shattuck Hospital, Commonwealth of Massachusetts.

4:15 Asymptomatic Gastric Retention—Gastroparesis Diabeticorum—in Moderately Severe Diabetics.
Paul Kassander, (Associate), Manchester, N. H.
Chief, Medical Service, Veterans Administration Hospital.

4:25 The Diagnosis of Small Bowel Tumors.
James F. Patterson, (Associate), Boston, Mass.
Assistant Professor of Medicine, Tufts University School of Medicine.
Allan D. Callow, M.D., (by invitation), Boston, Mass.
Assistant Professor of Surgery, Tufts University School of Medicine.
Alice Ettinger, M.D., (by invitation), Boston, Mass.
Clinical Professor of Radiology, Tufts University School of Medicine.

4:35 The Evaluation of the Present Day Therapeutic Approach to the Management of Regional Enteritis.
J. A. Bargen, F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation).

4:50 Studies on the Pathogenesis of Manson's Schistosomiasis.
R. S. Diaz-Rivera, F.A.C.P., San Juan, P. R.
Professor and Head, Department of Medicine, University of Puerto Rico School of Medicine.

Z. R. Sotomayor, M.D., (by invitation), San Juan, P. R.
Assistant in Medicine, University of Puerto Rico School of Medicine.
A. A. Cintrón-Rivera, M.D., (by invitation), San Juan, P. R.
Assistant Professor of Medicine (Therapeutics) and Director of Clinical Research Laboratory, University of Puerto Rico School of Medicine.

5:00 ADJOURNMENT.

Thursday Evening, April 11, 1957

7:00 o'Clock

Georgian Room, Hotel Statler

"DUTCH TREAT" COCKTAIL PARTY

8:00 o'Clock

Imperial Ballroom

THE ANNUAL BANQUET OF THE COLLEGE

Music by Ruby Newman

Toastmaster

Howard B. Sprague, F.A.C.P.

Speaker

Prof. Allan R. Foley

"Tales from the Vermont Hills"

Procure tickets at the Registration Bureau, Mechanics' Building, before 3:00 P.M., Wednesday. Tickets will be assigned by tables and those wishing to sit together must apply together or on a single application.

FIFTH GENERAL SESSION

Grand Hall, Mechanics' Building

Friday Afternoon, April 12, 1957

Presiding Officer

Richard P. Stetson, F.A.C.P., Boston, Mass.
Governor, A.C.P.

P.M.

2:00 **Our Growing Understanding of Thyroid Function and Its Clinical Applications.**
James H. Means, F.A.C.P., Boston, Mass.
Past President, A.C.P.; Jackson Professor of Clinical Medicine, Emeritus, Harvard University.

2:30 **Exophthalmos of Graves' Disease: Present Clinical Status.**
E. Perry McCullagh, F.A.C.P., Cleveland, Ohio.
Head of Section, Department of Endocrinology and Metabolism, Cleveland Clinic.

2:45 The Immuno-Hematologic Aspects of Disseminated Lupus.
WILLIAM DAMESHEK, F.A.C.P., Boston, Mass.
Professor of Medicine, Tufts University School of Medicine; Senior Physician and Chief of Hematology, New England Center Hospital.

3:00 Jaundice, Hyperlipemia, and Hemolytic Anemia—A Heretofore Unrecognized Syndrome Associated with Alcoholic Fatty Liver or Cirrhosis.
LESLIE ZIEVE, (Associate), Minneapolis, Minn.
Associate Professor of Medicine, University of Minnesota Medical School; Director, Radioisotope Unit (Research) and Staff Consultant in Medicine, Veterans Administration Hospital.

3:15 Evidences for Clinical Magnesium Deficiency.
E. B. FLINK, F.A.C.P., Minneapolis, Minn.
Associate Professor of Medicine, University of Minnesota Medical School; Chief of Medical Service, Veterans Administration Hospital.
ANANDA PRASAD, M.D., (by invitation), Minneapolis, Minn.
Fellow, Department of Medicine, University of Minnesota Medical School.

3:30 Hypoventilation Syndrome as a Clinical Problem: Physiologic Studies in Selected Cases.
E. OSBORNE COATES, JR., (Associate), Detroit, Mich.
Physician-in-charge, Pulmonary Division, Henry Ford Hospital.
GEOFFREY L. BRINKMAN, M.D., (by invitation), Detroit, Mich.
Associate Physician, Pulmonary Division, Henry Ford Hospital.

3:45 ADJOURNMENT.

MORNING LECTURES

There are Lectures on Wednesday and Friday mornings These are planned to present fundamental subjects and problems and to enable the speaker to cover his presentation fully with adequate slides and other media of illustration.

They are open to all members and guests of the College by regular registration badge; no special tickets.

Wednesday, April 10, 1957

Grand Hall, Mechanics' Building

Presiding Officer

Wallace M. Yater, F.A.C.P., Washington, D. C.
Secretary-General, A.C.P.

A.M.

9:00 Farmers' Daughters and Cancer Research.
HARRY S. N. GREENE, M.D., (by invitation), New Haven, Conn.
The Anthony N. Brady Professor of Pathology, Yale University School of Medicine.

9:40 Research for the Patient with Cancer.
SIDNEY FARBER, M.D., (by invitation), Boston, Mass.
Director of Research, The Children's Cancer Research Foundation; Professor of Pathology, Harvard Medical School.

10:20 **The Role of the Internist in the Treatment of Cancer.**
RALPH JONES, JR., (Associate), Miami, Fla.
Professor and Chairman of the Department of Medicine, University of Miami School of Medicine.

10:40 **Some General Concepts Applying to the Clinical Use of Radioisotopes.**
GOULD A. ANDREWS, (Associate), Oak Ridge, Tenn.
Chief of Clinical Services, Oak Ridge Institute of Nuclear Studies.

11:00 ADJOURNMENT.

Friday, April 12, 1957

Grand Hall, Mechanics' Building

Presiding Officer

Asa L. Lincoln, F.A.C.P., New York, N. Y.
Regent, A.C.P.

A.M.

9:00 **Medical Ophthalmology.**
SAMUEL A. SHELBURNE, F.A.C.P., Dallas, Tex.
Associate Professor of Medicine, Southwestern Medical School of University of Texas.

9:20 **Diagnostic and Prognostic Significance of the Vascular Retinopathies as Revealed by Serial Color Photographs.**
ALBERT A. BRUST, (Associate), Atlanta, Ga.
Associate Professor of Medicine, Emory University School of Medicine.

9:40 **Experience with the Interaction of Heart Disease and Pregnancy.**
C. SIDNEY BURWELL, F.A.C.P., Boston, Mass.
Samuel A. Levine Professor of Medicine, Harvard Medical School.
JAMES METCALFE, M.D., (by invitation), Boston, Mass.
Associate in Medicine, Harvard Medical School.

10:20 **The Nephrotic Syndrome in Adults; a Common Cause of Many Diseases.**
ROBERT M. KARK, F.A.C.P., Chicago, Ill.
Professor of Medicine, University of Illinois College of Medicine.
CONRAD L. PIRANI, M.D., (by invitation), Chicago, Ill.
Professor of Pathology, University of Illinois College of Medicine.
VICTOR E. POLLAK, M.B., (by invitation), Chicago, Ill.
Instructor in Medicine, University of Illinois College of Medicine.
ROBERT C. MUEHRCKE, M.D., (by invitation), Chicago, Ill.
Clinical Instructor in Medicine, University of Illinois College of Medicine.
JOHN D. BLAINEY, M.D., (by invitation), Chicago, Ill.
Research Associate in Medicine, University of Illinois College of Medicine.

10:40 **Diagnosis, Pathogenesis and Treatment of Pyelonephritis.**
GEORGE GEE JACKSON, (Associate), Chicago, Ill.
Associate Professor of Medicine, University of Illinois College of Medicine.

11:00 ADJOURNMENT.

THE SYMPOSIA

Following intermission of the General Sessions, after which the General Session in the Grand Hall will continue, there will be two Symposia Monday through Thursday, one in Paul Revere Hall, one in Talbot Hall. In these Symposia there will be a more exhaustive presentation of the several subjects by groups of authoritative speakers than the more formal presentations in the General Sessions and Morning Lectures permit.

Admission by regular registration badge; no special tickets required.

SYMPOSIA

Paul Revere Hall, Mechanics' Building

ARTHRITIS

Monday, April 8, 1957

3:45–5:00 P.M.

Moderator

William D. Robinson, F.A.C.P., Ann Arbor, Mich.
Professor of Internal Medicine, University of Michigan Medical School

P.M.

3:45 Non-Articular Rheumatism.
WALLACE GRAHAM, M.D., F.R.C.P., (by invitation), Toronto, Ont.
Assistant Professor of Medicine, University of Toronto Faculty of Medicine.

4:00 The Biochemist's Contribution to the Understanding of Diseases of Connective Tissue.
EVAN CALKINS, M.D., (by invitation), Boston, Mass.

4:15 The Significance of the LE Phenomenon in Diseases of Connective Tissue.
JOHN R. HASERICK, F.A.C.P., Cleveland, Ohio.
Associate Professor of Dermatology, Frank E. Bunts Educational Institute, Cleveland Clinic Foundation.

4:30 Indications for and the Choice of Adrenal Corticosteroids in the Management of Rheumatoid Arthritis.
JOSEPH J. BUNIM, F.A.C.P., Bethesda, Md.
Clinical Director, National Institute of Arthritis and Metabolic Diseases.

4:45 Discussion.

SYMPOSIA

Talbot Hall, Mechanics' Building

ALCOHOLISM: A COMPLEX MEDICAL PROBLEM

Monday, April 8, 1957

3:45–5:00 P.M.

Moderator

William C. Menninger, F.A.C.P., Topeka, Kans.
Professor of Clinical Psychiatry, University of Kansas School of Medicine; Governor, A.C.P.

P.M.

3:45 **Diseases Associated with Alcoholism.**
ROBERT M. KARK, F.A.C.P., Chicago, Ill.
Professor of Medicine, University of Illinois College of Medicine.

4:00 **Social Factors in Alcoholism.**
SELDEN D. BACON, Ph.D., (by invitation), New Haven, Conn.
Professor of Sociology, Yale University; Director, Yale Center of Alcohol Studies; Chairman, Connecticut Commission on Alcoholism.

4:25 **Psychological Factors in Chronic Alcoholism.**
ROBERT WALLERSTEIN, (Associate), Topeka, Kans.
Associate Director of Research, Menninger Foundation.

4:50 **Discussion.**

SYMPOSIA

Paul Revere Hall, Mechanics' Building

DISEASES OF THE LARGE ARTERIES

Tuesday, April 9, 1957

3:45–5:00 P.M.

Moderator

Hugh Montgomery, F.A.C.P., Philadelphia, Pa.
Associate Professor of Medicine, University of Pennsylvania School of Medicine

P.M.

3:45 **An Approach to the Etiology, Diagnosis and Management of Peripheral Arteriosclerosis.**
WILLIAM E. JAHSMAN, F.A.C.P., Detroit, Mich.
Physician-in-charge, Medical Clinic No. 2, Henry Ford Hospital.

4:00 **Occlusion of the Abdominal Aorta and Iliac Arteries: A Study of 105 Cases.**
J. EARLE ESTES, F.A.C.P., Rochester, Minn.
Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine, Section of Peripheral Vascular Diseases, Mayo Clinic.
JOHN J. MASSARELLI, JR., M.D., (by invitation), Rochester, Minn.
Fellow in Medicine, University of Minnesota (Mayo Foundation).

4:15 **Considerations in Selecting Patients for Arterial Grafting in Chronic Peripheral Arterial Occlusion.**
ORVILLE HORWITZ, F.A.C.P., Philadelphia, Pa.
Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.
RAYMOND PENNEYS, M.D., (by invitation), Philadelphia, Pa.
Associate in Medicine, University of Pennsylvania School of Medicine.

4:30 **Observations in the Management of Later Arteriosclerosis Obliterans.**
HARVEY L. MYERS, F.A.C.P., Cedarhurst, N. Y.
Clinical Associate in Medicine, New York Medical College, Flower and Fifth Avenue Hospitals.

4:45 **Discussion.**

SYMPOSIA

Talbot Hall, Mechanics' Building

DISEASES OF INTESTINAL ABSORPTION

Tuesday, April 9, 1957

3:45–5:00 P.M.

Moderator

Chester M. Jones, F.A.C.P., Boston, Mass.

Clinical Professor of Medicine, Harvard Medical School; First Vice President, A.C.P.

P.M.

3:45 The Differential Diagnosis of Pancreatic Insufficiency and the Malabsorption Syndromes.

B. J. Duffy, Jr., (Associate), Washington, D. C.
Assistant Professor of Medicine, Georgetown University School of Medicine.

D. A. Turner, Ph.D., (by invitation), Washington, D. C.
Georgetown University Medical Center.

R. J. Coffey, M.D., (by invitation), Washington, D. C.
Professor of Surgery and Director of the Department of Surgery, Georgetown University School of Medicine.

3:55 Intestinal Biopsies in Sprue.

Charles E. Butterworth, Jr., M.D., (by invitation), San Juan, P. R.
Major, (M.C.), U.S.A.; Tropical Research Medical Laboratory.

Enrique Perez-Santiago, M.D., (by invitation), San Juan, P. R.
Assistant Clinical Professor of Medicine, University of Puerto Rico School of Medicine.

4:05 Malabsorption Syndrome and Pernicious Anemia: Analysis of the Defect in Vitamin B-12 Absorption.

David Adlersberg, F.A.C.P., New York, N. Y.
Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons.

Sanford Oxenhorn, M.D., (by invitation), New York, N. Y.
Research Fellow in Hematology, The Mount Sinai Hospital.

4:15 Differentiation of Macrocytic Anemias and Detection of Pernicious Anemia and Sprue in Remission by Accelerated Measurement of Hepatic Uptake of Radioactive Co60 B-12.

George B. Jerzy Glass, F.A.C.P., New York, N. Y.
Associate Professor of Medicine, New York Medical College.

4:25 The Effect of Adrenocortical Steroids on the Absorption of Vitamin B-12 in Patients with Malabsorption Syndromes.

John W. Frost, F.A.C.P., Philadelphia, Pa.
Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.

Manfred I. Goldwein, M.D., (by invitation), Philadelphia, Pa.
Assistant Instructor in Medicine, University of Pennsylvania School of Medicine.

Barre D. Kaufman, M.D., (by invitation), Capt., (MC), U.S.A.

4:35 Discussion.

SYMPOSIA

Paul Revere Hall, Mechanics' Building

THE PATHOGENESIS OF CORONARY HEART DISEASE

Wednesday, April 10, 1957

3:45–5:00 P.M.

Moderator

David P. Barr, M.A.C.P., New York, N. Y.
Past President, A.C.P.; Professor of Medicine, Cornell University Medical College; Physician-in-chief, New York Hospital.

P.M.

3:45 The Influence of Gonadal Hormones on Serum Lipids and Lipoproteins; Studies in Normal, Hypogonadal Subjects and in Eunuchs.
ROBERT H. FURMAN, F.A.C.P., Oklahoma City, Okla.
Head of Cardiovascular Section, Oklahoma Medical Research Foundation.
R. PALMER HOWARD, F.A.C.P., Oklahoma City, Okla.
Associate Professor of Research Medicine, University of Oklahoma School of Medicine.

3:55 Estrogen Replacement Therapy in Women with Coronary Atherosclerosis.
ROGER W. ROBINSON, (Associate), Worcester, Mass.
Chief of Medical Service and Cardiologist, Memorial Hospital.
WILLIAM D. COHEN, Ph.D., (by invitation), Worcester, Mass.
NORIO HIGANO, M.D., (by invitation), Worcester, Mass.
Memorial Hospital.

4:05 Lessons from Serum Cholesterol Studies in Japan, Hawaii and Los Angeles.
ANCEL KEYS, Ph.D., (by invitation), Minneapolis, Minn.
Director, Laboratory of Physiological Hygiene, University of Minnesota.

4:20 Optimal Intake of Dietary Fat; Quality vs. Quantity.
E. H. AHRENS, JR., M.D., (by invitation), New York, N. Y.
JULES HIRSCH, M.D., (by invitation), New York, N. Y.
WILLIAM INSULL, JR., M.D., (by invitation), New York, N. Y.
T. T. TSALTAS, M.D., (by invitation), New York, N. Y.
R. L. BLOMSTRAND, M.D., (by invitation), New York, N. Y.
MALCOLM PETERSON, M.D., (by invitation), New York, N. Y.
Hospital of the Rockefeller Institute for Medical Research.

4:45 Discussion.

SYMPOSIA

Talbot Hall, Mechanics' Building

TREATMENT OF TUBERCULOSIS

Wednesday, April 10, 1957

3:45–5:00 P.M.

Moderator

Robert H. Ebert, F.A.C.P., Cleveland, Ohio
Chairman, Department of Medicine, Western Reserve University

P.M.

3:45 Changing Concepts in the Treatment of Tuberculosis.
IRVING KASS, (Associate), Denver, Colo.
Assistant Medical Director, National Jewish Hospital at Denver.

3:55 In-Patient Ambulatory Treatment of Tuberculosis.
JAMES A. WIER, Colonel, (MC), U.S.A., F.A.C.P., Denver, Colo.
Chief, Pulmonary Disease Service, Fitzsimons Army Hospital.
R. L. TAYLOR, (MSC), U.S.A., (by invitation), Denver, Colo.
O. L. WEISER, M.D., (by invitation), Denver, Colo.
R. S. FRASER, Lieutenant Colonel, (MC), U.S.A., (by invitation), Denver, Colo.
Pulmonary Disease Service and Research and Development Service, Fitzsimons Army Hospital.

4:05 The Place of Drug Therapy in the Management of Unhospitalized Tuberculosis Patients.
ARTHUR B. ROBINS, F.A.C.P., New York, N. Y.
Director, Bureau of Tuberculosis, New York City Department of Health.

4:15 Treatment of Tuberculous Meningitis with a Combination of Izonicotinic Acid Hydrazides, Streptomycin and Para-Amino-Salicylic Acid.
EMANUEL APPELBAUM, F.A.C.P., New York, N. Y.
Chief of the Division of Acute Infections of the Central Nervous System, New York City Department of Health.
CHARLES ABLER, M.D., (by invitation), New York, N. Y.

4:25 Treatment Failures in the Management of Tuberculosis.
THEODORE L. BADGER, F.A.C.P., Boston, Mass.
Assistant Clinical Professor of Medicine, Harvard Medical School.

4:45 Discussion.

SYMPOSIA

Paul Revere Hall, Mechanics' Building

GASTRODUODENAL ULCER

Thursday, April 11, 1957

3:45–5:00 P.M.

Moderator

Sara M. Jordan, F.A.C.P., Boston, Mass.
Director, Department of Gastro-enterology, Lahey Clinic

P.M.

3:45 Gastric Secretion as Influenced by Rauwolfia Alkaloids.
EDWARD M. SCHNEIDER, (Associate), Oklahoma City, Okla.
Assistant Professor of Medicine, University of Oklahoma School of Medicine.
M. L. CLARK, M.D., (by invitation), Oklahoma City, Okla.
Assistant Professor of Medicine, University of Oklahoma School of Medicine.

3:55 Acute Peptic Ulceration Following Cardiac Surgery.

DONALD BERKOWITZ, M.D., (by invitation), Philadelphia, Pa.
Departments of Medicine and Thoracic Surgery, Hahnemann Medical College.
BERNARD M. WAGNER, M.D., (by invitation), Philadelphia, Pa.
Associate Pathologist, Children's Hospital.
JOSEPH F. URICCHIO, M.D., (by invitation), Philadelphia, Pa.
Cardiologist, Bailey Thoracic Clinic.

4:05 The Effect of X-Ray Therapy on Gastric Acidity, 17-Hydroxycorticoids and Uropepsin Excretion.

J. ALFRED RIDER, (Associate), San Francisco, Calif.
Assistant Professor of Medicine, University of California Medical Center.
HUGO C. MOELLER, M.D., (by invitation), San Francisco, Calif.
Assistant Professor of Medicine, University of California Medical Center.
GLENN E. SHELINE, M.D., (by invitation), San Francisco, Calif.
Assistant Professor of Radiology, University of California Medical Center.
THEODORE L. ALTHAUSEN, F.A.C.P., San Francisco, Calif.
Professor of Medicine, University of California Medical Center.

4:15 Drug Induced Peptic Ulcer.

JOSEPH B. KIRSNER, F.A.C.P., Chicago, Ill.
Professor of Medicine, University of Chicago School of Medicine.

4:25 Postbulbar Duodenal Ulcers.

JAMES C. CAIN, F.A.C.P., Rochester, Minn.
Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine, Mayo Clinic.
LLOYD G. BARTHOLOMEW, M.D., (by invitation), Rochester, Minn.
Section of Medicine, Mayo Clinic.
GEORGE D. DAVIS, M.D., (by invitation), Rochester, Minn.
Section of Roentgenology, Mayo Clinic.

4:35 The Efficacy of Medical Criteria in Differentiating Benign from Malignant Gastric Ulcers.

HARVEY J. DWORKEN, (Associate), Cleveland, Ohio.
Clinical Instructor in Medicine, Western Reserve University School of Medicine.
HAROLD P. ROTH, F.A.C.P., Cleveland, Ohio.
Assistant Professor of Medicine, Western Reserve University School of Medicine.
HERBERT C. DUBER, M.D., (by invitation), Cleveland, Ohio.
Assistant Physician, Mount Sinai Hospital.

4:45 Discussion.

SYMPOSIA

Talbot Hall, Mechanics' Building

REHABILITATION

Thursday, April 11, 1957

3:45–5:00 P.M.

Moderator

S. D. Pomrinse, (Associate), Washington, D. C.

Chief, Health of the Aged, Chronic Disease Program, Division of Special Health Services, Department of Health, Education and Welfare

P.M.

3:45 The Role of the Internist in Restorative Services for the Aged.
S. D. Pomrinse, (Associate), Washington, D. C.

4:00 Rehabilitation as Related to Internal Medicine.
Harold N. Willard, (Associate), New York, N. Y.
Coordinator, Rehabilitation Program, The New York Hospital, Cornell Medical Center.

4:15 Physical Medicine and Rehabilitation: Effectiveness and Progress in Restoration of the Chronically Ill and Aging.
A. B. C. Knudson, F.A.C.P., Washington, D. C.
Director, Physical Medicine and Rehabilitation Service, Veterans Administration.

4:30 Muscular Dystrophy: Diagnosis, Prognosis and Evaluation: Management by Physical Medicine and Rehabilitation.
M. K. Newman, F.A.C.P., Detroit, Mich.
Director of Physical Medicine and Rehabilitation, Sinai Hospital.

4:45 Clinical Management and Rehabilitation of the Long Term Patient with Respiratory Insufficiency.
Joseph G. Benton, F.A.C.P., New York, N. Y.
Associate Professor of Clinical Physical Medicine and Rehabilitation, Coordinator of Education and Research, New York University College of Medicine.

CLINICAL PATHOLOGICAL CONFERENCES

on the

APPLICATION OF THE BASIC SCIENCES TO CLINICAL MEDICINE

Each day Tuesday through Friday, in the Grand Hall, Mechanics' Building, from 11:40 A.M. to 1:00 P.M., selected clinical subjects will be presented and discussed. In the discussion the fundamental mechanisms and processes in relation to the clinical manifestations of the disorder under consideration will be developed. The participants in these conferences are clinicians, but they are also recognized for their investigative abilities and contributions in their particular fields of medicine. This type of conference is new to the College program and is being offered to bring to the clinician the application of the basic sciences to the practice of internal medicine.

The protocols of the case to be discussed will be published in the final program.

No special tickets required, other than general registration badge.

CLINICAL PATHOLOGICAL CONFERENCES ON THE APPLICATION OF THE BASIC SCIENCES TO CLINICAL MEDICINE

Grand Hall, Mechanics' Building

	Tuesday, April 9, 1957	Wednesday, April 10, 1957	Thursday, April 11, 1957	Friday, April 12, 1957
11:40 A.M. to 1:00 P.M.	**Problems in Impaired Intestinal Absorption** **Chairman** Chester M. Jones, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School **Participants** John A. Benson, Jr., (by invitation), Instructor in Medicine, Harvard Medical School. Stanley L. Robbins, (by invitation), Associate Professor of Pathology, Boston University School of Medicine. Eric E. Wollaeger, (by invitation), Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine, Mayo Clinic, Rochester, Minn. --- Two cases will be discussed demonstrating the clinical problems encountered in malabsorption and its resultant deficiency states from long-continued disease of the small bowel due to different causes.	**Anemia** **Chairman** William B. Castle, F.A.C.P., Professor of Medicine, Harvard Medical School. **Participants** Allan J. Erslev, (by invitation), Associate in Medicine, Harvard Medical School. Frank H. Gardner, (by invitation), Associate in Medicine, Harvard Medical School. James H. Jandl, (by invitation), Instructor in Medicine, Harvard Medical School. John W. Harris, (by invitation), Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio. Carl V. Moore, F.A.C.P., Busch Professor of Medicine, Washington University School of Medicine, St. Louis, Mo. Richard W. Vilter, F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio. --- The mechanisms and pathological physiology involved in the production of hemolytic anemia, macrocytic anemia and hypochromic anemia will be discussed as illustrated by three cases.	**Hirsutism in the Female** **Chairman** George W. Thorn, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School **Participants** Gustave J. Dammin, (by invitation), Professor of Pathology at the Peter Bent Brigham Hospital. Don H. Nelson, (by invitation), Research Associate in Medicine, Harvard Medical School. Albert E. Renold, (by invitation), Instructor in Medicine, Harvard Medical School. Somers H. Sturgis, (by invitation), Associate Professor of Gynecology, Harvard Medical School. --- Abnormal hair distributions in girls and women is a common disorder and may be dependent upon adrenal, ovarian, pituitary or constitutional factors. Rational procedures indicated in the studies leading to a fundamental diagnosis and the establishment of a rationale of therapy will be developed.	**Clinical Pathological Conference** **Discusser** Chester S. Keefer, F.A.C.P., Wade Professor of Medicine, Boston University School of Medicine **Radiologist** Richard Schatzki, (by invitation), Clinical Associate in Radiology and Roentgenologist, Department of Hygiene, Harvard University. **Pathologist** Gustave J. Dammin, (by invitation), Professor of Pathology at the Peter Bent Brigham Hospital. --- The case history to be discussed will be published in the final program so that members may have the opportunity of venturing their own diagnoses—to be confirmed or denied by the eventual disclosures of the pathologist.

PANEL DISCUSSIONS

Topics of intimate interest and practical value to all members of the College have been chosen. Qualified men have been selected as Moderators and Panelists. All Panels are scheduled from Tuesday through Friday, from 11:40 A.M. to 1:00 P.M., at places indicated on the following chart.

Tickets will be required for certain Panels as indicated in the headings of the chart. Where capacities are limited, admission by ticket will be enforced. Applications for tickets to Panels may be made in advance by MEMBERS on a regular application form which will accompany the final program. Tickets will also be available at the Registration Bureau, Mechanics' Building. NON-MEMBERS may not register for Panels by mail, but should secure their tickets directly at the Registration Bureau at the meeting.

Members may submit in writing three weeks before the Session, through the Executive Secretary of the College, questions concerning any phase of the subjects listed. The application form for tickets will also provide space on which to fill in these questions. Moderators and Panelists will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions, including questions from the floor, as time permits.

PANEL DISCUSSIONS

	Sheraton Plaza Ballroom (Admission by badge; no tickets)	Sheraton Plaza Oval Room (Admission by ticket only)	Mechanics' Building Revere Hall (Admission by ticket only)	Mechanics' Building Talbot Hall (Admission by ticket only)	Mechanics' Building Paul Revere Banquet Hall (Admission by ticket only)
Capacity	1,000	500	480	400	250
Tuesday April 9 11:40 A.M. to 1:00 P.M.	**P-1** **Relationship of Heart Disease to Injury, Stress, and Occupation** Moderator **Paul D. White Boston Milton Helpern New York *Howard A. Rusk New York Bryan Williams Dallas	**P-2** **Medical Management of Malignant Disease** Moderator Sidney Farber Boston *Charles A. Doan Columbus *Alfred Gellhorn New York *Olof H. Pearson New York	**P-3** **Anticoagulant Therapy** Moderator *Irving S. Wright New York Benjamin Alexander Boston Eugene A. Clifton New York *George C. Griffith Los Angeles	**P-4** **Reversible Renal Failure** Moderator *Maurice B. Strauss Boston Franklin H. Epstein New Haven William B. Schwartz, Jr. Boston †Paul E. Teschan M. C., U. S. Army	
Wednesday April 10 11:40 A.M. to 1:00 P.M.	**P-5** **Purpura and Other Autoimmune Mechanisms** Moderator *William Dameshek Boston †William H. Crosby, Jr. Washington †William J. Harrington St. Louis *Scott N. Swisher, Jr. Rochester, N. Y.	**P-6** **Laboratory Diagnosis of Endocrine Disorders** Moderator *Edward H. Rynearson Rochester Joseph W. Jailer New York John MacLeod New York Somers H. Sturgis Boston	**P-7** **Oral Hypoglycemic Compounds in the Treatment of Diabetes Mellitus** Moderator *Alexander Marble Boston *Arthur R. Colwell Chicago *Garfield G. Duncan Philadelphia Rachmiel Levine Chicago	**P-8** **Factors Influencing Resistance to Infection** Moderator *Yale Kneeland, Jr. New York *Paul B. Beeson New Haven Charles A. Janeway Boston *Louis Weinstein Boston	**P-9** **Idiosyncratic Drug Reactions** Moderator *William B. Sherman New York Harry Beckman Milwaukee *Robert P. McCombs Boston *Bram Rose Montreal

** M.A.C.P. * F.A.C.P. † Associate.

PANEL DISCUSSIONS

	Sheraton Plaza Ballroom (Admission by badge; no tickets)	Sheraton Plaza Oval Room (Admission by ticket only)	Mechanics' Building Revere Hall (Admission by ticket only)	Mechanics' Building Talbot Hall (Admission by ticket only)	Mechanics' Building Paul Revere Banquet Hall (Admission by ticket only)
Capacity	1,000	500	480	400	250
Thursday April 11 11:40 A.M. to 1:00 P.M.	**P-10 Hepatic Coma** Moderator *Henry L. Bockus Philadelphia Samuel P. Bessman Baltimore *Hugh R. Butt Rochester William V. McDermott Boston *Leon Schiff Cincinnati	**P-11 Electrocardiographic Conference** Moderator *Charles E. Kossmann New York Robert P. Grant Bethesda *Hans H. Hecht Salt Lake City Raymond D. Pruitt Rochester	**P-12 Usefulness of Pulmonary Function Tests** Moderator *Julius H. Comroe, Jr. Philadelphia *Ronald V. Christie Montreal *Lewis Dexter Boston Edward A. Gaensler Boston	**P-13 Present-day Treatment of Thyroid Diseases** Moderator *Rulon W. Rawson New York *Elmer C. Bartels Boston A. Stone Freedberg Boston Lawrence W. Sloan New York	**P-14 Gout** Moderator *John H. Talbott Buffalo *Theodore B. Bayles Boston *Charley J. Smyth Denver DeWitt Stetten, Jr. Bethesda
Friday April 12 11:40 A.M. to 1:00 P.M.			**P-15 Regional Enteritis** Moderator *Burrill B. Crohn New York Claude F. Dixon Rochester *Seymour J. Gray Boston Richard H. Marshak New York Samuel F. Marshall Boston	**P-16 Management of the Nephrotic Syndrome** Moderator *George W. Thorn Boston Henry L. Barnett New York †Arthur J. Merrill Atlanta Arnold S. Relman Boston	**P-17 Nutritional and Metabolic Disorders of the Nervous System** Moderator Joseph M. Foley Boston *George D. Gammon Philadelphia Richard B. Richter Chicago L. Lahut Uzman Boston

* F.A.C.P. † Associate.

TUESDAY, April 9

11:40 A.M.–1:00 P.M.

Panel P-1

Sheraton Plaza Ballroom

Relationship of Heart Disease to Injury, Stress, and Occupation.

Moderator: PAUL D. WHITE, M.A.C.P., Boston.
Consultant in Medicine, Massachusetts General Hospital, and Consultant, National Heart Institute.

MILTON HELPERN, M.D., (by invitation), New York.
Associate Professor of Forensic Medicine, New York University Post-Graduate Medical School.

HOWARD A. RUSK, F.A.C.P., New York.
Professor of Physical Medicine and Rehabilitation, New York University College of Medicine.

BRYAN WILLIAMS, M.D., (by invitation), Dallas.
Clinical Instructor in Medicine, University of Texas Southwestern Medical School.

More requests were received for a discussion of these controversial relationships of injury, stress, and occupation to heart disease than for any other topic. The panel members have had an unusually broad experience in this regard. They will discuss both the etiological and the therapeutic aspects of patients with such potentially related disorders.

TUESDAY, April 9

11:40 A.M.–1:00 P.M.

Panel P-2

Sheraton Plaza Oval Room

Medical Management of Malignant Disease.

Moderator: SIDNEY FARBER, M.D., (by invitation), Boston.
Professor of Pathology, Children's Medical Center, Harvard Medical School, and Director of the Children's Cancer Research Foundation.

CHARLES A. DOAN, F.A.C.P., Columbus.
Dean and Professor of Medicine, Ohio State University College of Medicine; Governor of American College of Physicians, Ohio.

ALFRED GELLHORN, F.A.C.P., New York.
Associate Professor of Medicine, Columbia University College of Physicians and Surgeons.

OLOF H. PEARSON, F.A.C.P., New York.
Associate Professor of Clinical Medicine, Cornell University Medical College.

A discussion of medical therapy of malignant states including chemotherapy, hormone therapy, and protein catabolism.

TUESDAY, April 9

11:40 A.M.–1:00 P.M.

Panel P-3

Revere Hall, Mechanics' Building

Anticoagulant Therapy: Present and Future.

Moderator: Irving S. Wright, F.A.C.P., New York.
Professor of Clinical Medicine, Cornell University Medical College; Governor of American College of Physicians, Eastern New York.

Benjamin Alexander, M.D., (by invitation), Boston.
Associate Professor of Medicine, Harvard Medical School.

Eugene E. Clifton, M.D., (by invitation), New York.
Associate Professor of Clinical Surgery, Cornell University Medical College.

George C. Griffith, F.A.C.P., Los Angeles.
Professor of Medicine, University of Southern California School of Medicine; Governor of American College of Physicians, Southern California.

A critical reappraisal of the role of anticoagulants in present-day therapy with particular reference to new agents currently under study.

TUESDAY, April 9

11:40 A.M.–1:00 P.M.

Panel P-4

Talbot Hall, Mechanics' Building

Reversible Renal Failure.

Moderator: Maurice B. Strauss, F.A.C.P., Boston.
Professor of Clinical Medicine, Boston University School of Medicine; Lecturer in Medicine, Harvard Medical School and Tufts University School of Medicine.

Franklin H. Epstein, M.D., (by invitation), New Haven.
Assistant Professor of Medicine, Yale University School of Medicine.

William B. Schwartz, Jr., M.D., (by invitation), Boston.
Assistant Professor of Medicine, Tufts University School of Medicine.

Paul E. Teschan, (Associate), Major, (MC), U. S. Army.
Chief, Renal Division, Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Tex.

The means by which the physician may recognize the several reversible types or degrees of renal failure and separate these from those renal disorders for which no treatment exists will be reviewed. The specific therapy for the former will then be discussed in detail.

WEDNESDAY, April 10

11:40 A.M.–1:00 P.M.

Panel P-5

Sheraton Plaza Ballroom

Purpura and Other Autoimmune Mechanisms.

Moderator: William Dameshek, F.A.C.P., Boston.
Professor of Medicine, Tufts University School of Medicine.

William H. Crosby, Jr., (Associate), Washington.
Chief, Department of Hematology, Army Medical Service Graduate School.

WILLIAM J. HARRINGTON, (Associate), St. Louis.
Assistant Professor of Medicine, Washington University School of Medicine.

SCOTT N. SWISHER, JR., F.A.C.P., Rochester.
Assistant Professor of Medicine, University of Rochester School of Medicine.

A review of autoimmune hematologic disorders: purpura, agranulocytosis and acquired hemolytic anemia, which may appear in the course of diverse medical diseases.

WEDNESDAY, April 10

11:40 A.M.–1:00 P.M.

Panel P-6

Sheraton Plaza Oval Room

Laboratory Diagnosis of Endocrine Disorders.

Moderator: EDWARD H. RYNEARSON, F.A.C.P., Rochester.
Chairman of Section on Endocrinology and Metabolism, Mayo Clinic.

JOSEPH W. JAILER, M.D., (by invitation), New York.
Associate Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons.

JOHN MACLEOD, M.D., (by invitation), New York.
Associate Professor of Physiology, Cornell University Medical College.

SOMERS H. STURGIS, M.D., (by invitation), Boston.
Clinical Professor of Gynecology, Harvard Medical School.

The establishment of a diagnosis of a disordered function of adrenal, ovary, or testicle is often excessively consuming in time and tissue to physician and patient, respectively. The panel will review the indications for laboratory tests related to these organs, the specific tests needed to establish the diagnosis in question, and the current or future simplifications of some of our most complicated endocrinological diagnostic procedures.

WEDNESDAY, April 10

11:40 A.M.–1:00 P.M.

Panel P-7

Revere Hall, Mechanics' Building

Oral Hypoglycemic Compounds in the Treatment of Diabetes Mellitus.

Moderator: ALEXANDER MARBLE, F.A.C.P., Boston.
Assistant Clinical Professor of Medicine, Harvard Medical School.

ARTHUR R. COLWELL, F.A.C.P., Chicago.
Irving S. Cutter Professor of Medicine, Northwestern University Medical School.

GARFIELD G. DUNCAN, F.A.C.P., Philadelphia.
Clinical Professor of Medicine, Jefferson Medical College.

RACHMIEL LEVINE, M.D., (by invitation), Chicago.
Director, Department of Metabolism and Endocrine Research, Michael Reese Hospital.

During the past two years certain compounds have been found to be very useful in the treatment of specific types of diabetic patients, and others too hazardous for use. The panel will review their experiences with these drugs, the probable mechanisms involved in their action, and the future for newer oral compounds beneficial to the diabetic.

WEDNESDAY, April 10

11:40 A.M.–1:00 P.M.

Panel P-8

Talbot Hall, Mechanics' Building

Factors Influencing Resistance to Infection.

Moderator: YALE KNEELAND, JR., F.A.C.P., New York.
Associate Professor of Medicine, Columbia University College of Physicians and Surgeons.

PAUL B. BEESON, F.A.C.P., New Haven.
Ensign Professor of Medicine, Yale University School of Medicine.

CHARLES A. JANEWAY, M.D., (by invitation), Boston.
Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School.

LOUIS WEINSTEIN, F.A.C.P., Boston.
Associate Professor of Medicine, Boston University School of Medicine.

The exciting discoveries of substances such as properdin and other fundamental defenses against infections, and clinical and experimental evidence in indicating the importance of certain host factors in defense against infections will be discussed by the panel.

WEDNESDAY, April 10

11:40 A.M.–1:00 P.M.

Panel P-9

Paul Revere Banquet Hall, Mechanics' Building

Idiosyncratic Drug Reactions.

Moderator: WILLIAM B. SHERMAN, F.A.C.P., New York.
Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons.

HARRY BECKMAN, M.D., (by invitation), Milwaukee.
Professor of Pharmacology, Marquette University School of Medicine.

ROBERT P. MCCOMBS, F.A.C.P., Boston.
Professor of Graduate Medicine, Tufts University School of Medicine.

BRAM ROSE, F.A.C.P., Montreal.
Associate Professor of Medicine, McGill University Faculty of Medicine.

The large number of medicaments now in use present a formidable array of either toxic or allergic reactions in their use. The important clinical aspects and their recognition and treatment will be presented.

THURSDAY, APRIL 11

11:40 A.M.–1:00 P.M.

Panel P-10

Sheraton Plaza Ballroom

Hepatic Coma.

Moderator: HENRY L. BOCKUS, F.A.C.P., Philadelphia.
Professor of Medicine, University of Pennsylvania Graduate School of Medicine.

SAMUEL P. BESSMAN, M.D., (by invitation), Baltimore.
Assistant Clinical Professor of Pediatrics, University of Maryland School of Medicine.

HUGH R. BUTT, F.A.C.P., Rochester.
Professor of Medicine, University of Minnesota (Mayo Foundation).

WILLIAM V. MCDERMOTT, M.D., (by invitation), Boston.
Clinical Associate in Surgery, Harvard Medical School.

LEON SCHIFF, F.A.C.P., Cincinnati.
Professor of Clinical Medicine, University of Cincinnati College of Medicine.

The panel will discuss the progress recently made in understanding the disordered metabolism in hepatic coma. The practical application of these findings toward improved and vigorous management of the patient will be stressed.

THURSDAY, APRIL 11

11:40 A.M.–1:00 P.M.

Panel P-11

Sheraton Plaza Oval Room

Electrocardiographic Conference.

Moderator: CHARLES E. KOSSMANN, F.A.C.P., New York.
Associate Professor of Medicine, New York University College of Medicine.

ROBERT P. GRANT, M.D., (by invitation), Bethesda.
National Institutes of Health.

HANS H. HECHT, F.A.C.P., Salt Lake City.
L. E. Viko Professor of Cardiology, Department of Medicine, University of Utah College of Medicine.

RAYMOND D. PRUITT, M.D., (by invitation), Rochester.
Associate Professor of Medicine, University of Minnesota (Mayo Foundation).

A well-balanced panel of experts who will discuss recent advances in practical electrocardiography.

THURSDAY, APRIL 11

11:40 A.M.–1:00 P.M.

Panel P-12

Revere Hall, Mechanics' Building

Usefulness of Pulmonary Function Tests.

Moderator: JULIUS H. COMROE, JR., F.A.C.P., Philadelphia.
Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine.

RONALD V. CHRISTIE, F.A.C.P., Montreal.
Professor of Medicine, McGill University Faculty of Medicine.

EDWARD A. GAENSLER, M.D., (by invitation), Boston.
Clinical Associate in Surgery, Harvard Medical School.

LEWIS DEXTER, F.A.C.P., Boston.
Assistant Professor of Medicine, Harvard Medical School.

The information that the internist can obtain from clinically indicated pulmonary function tests will be stressed by the panel. The application of these findings to the patient and the implications in respect to surgery will receive special attention.

THURSDAY, APRIL 11

11:40 A.M.–1:00 P.M.

Panel P-13

Talbot Hall, Mechanics' Building

Present-day Treatment of Thyroid Diseases.

Moderator: RULON W. RAWSON, F.A.C.P., New York.
Professor of Medicine, Sloan-Kettering Division, Cornell University Medical College.

ELMER C. BARTELS, F.A.C.P., Boston.
Department of Internal Medicine, Lahey Clinic.

A. STONE FREEDBERG, M.D., (by invitation), Boston.
Assistant Professor of Medicine, Harvard Medical School.

LAWRENCE W. SLOAN, M.D., (by invitation), New York.
Associate Professor of Clinical Surgery, Columbia University College of Physicians and Surgeons.

The panel on Thyroid Disease will review the major disorders of thyroid function and, in the light of recent advances, will discuss the proper application of surgical, radiation, and medicinal techniques.

THURSDAY, APRIL 11

11:40 A.M.–1:00 P.M.

Panel P-14

Paul Revere Banquet Hall, Mechanics' Building

Gout.

Moderator: JOHN H. TALBOTT, F.A.C.P., Buffalo.
Professor of Medicine, University of Buffalo School of Medicine; Governor of American College of Physicians, Western New York.

THEODORE B. BAYLES, F.A.C.P., Boston.
Clinical Associate in Medicine, Harvard Medical School.

CHARLEY J. SMYTH, F.A.C.P., Denver.
Associate Professor of Internal Medicine, University of Colorado School of Medicine.

DEWITT STETTEN, JR., M.D., (by invitation), Bethesda.
National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

In the past few years there have been notable advances in the study of the metabolic disorder of gout and in the treatment of acute and chronic gouty arthritis. The metabolic derangement in the patient with gouty diathesis will be discussed. The current methods of present-day therapy will be presented.

FRIDAY, April 12

11:40 A.M.–1:00 P.M.

Panel P-15

Revere Hall, Mechanics' Building

Regional Enteritis.

Moderator: BURRILL B. CROHN, F.A.C.P., New York.
Consultant in Gastroenterology, Columbia University College of Physicians and Surgeons.

CLAUDE F. DIXON, M.D., (by invitation), Rochester.
Professor of Surgery, University of Minnesota (Mayo Foundation).

SEYMOUR J. GRAY, F.A.C.P., Boston.
Assistant Professor of Medicine, Harvard Medical School.

RICHARD H. MARSHAK, M.D., (by invitation), New York.
Associate Radiologist, Mount Sinai Hospital.

SAMUEL F. MARSHALL, M.D., (by invitation), Boston.
Surgeon, Lahey Clinic.

Since the Moderator of the panel first described this disorder 25 years ago, its increasing incidence is becoming apparent and the problems of its management increasingly important. Current speculations in regard to etiology, practical methods of diagnosis, and effectiveness of medical and surgical therapies will be considered in detail.

FRIDAY, April 12

11:40 A.M.–1:00 P.M.

Panel P-16

Talbot Hall, Mechanics' Building

Management of the Nephrotic Syndrome.

Moderator: GEORGE W. THORN, F.A.C.P., Boston.
Hersey Professor of Theory and Practice of Physic, Harvard Medical School.

HENRY L. BARNETT, M.D., (by invitation), New York.
Professor of Pediatrics, Albert Einstein College of Medicine.

ARTHUR J. MERRILL, (Associate), Atlanta.
Associate Professor of Medicine, Emory University School of Medicine.

ARNOLD S. RELMAN, M.D., (by invitation), Boston.
Associate Professor of Medicine, Boston University School of Medicine.

An increasing number of clinical disorders are being found which manifest themselves by a nephrotic syndrome. Certain of these can be greatly benefited by carefully planned therapy with steroids, others may be aggravated by this method of treatment. The panel will discuss the recognition of the basic etiological disorders and the indications for the proper treatment for that disease. Similarlities and differences between child and adult types will be considered.

FRIDAY, April 12

11:40 A.M.–1:00 P.M.

Panel P-17

Paul Revere Banquet Hall, Mechanics' Building

Nutritional and Metabolic Disorders of the Nervous System.

Moderator: JOSEPH M. FOLEY, M.D., (by invitation), Boston.
Assistant Professor of Neurology, Harvard Medical School.
GEORGE D. GAMMON, F.A.C.P., Philadelphia.
Professor of Clinical Neurology, University of Pennsylvania School of Medicine.
RICHARD B. RICHTER, M.D., (by invitation), Chicago.
Professor of Neurology, University of Chicago School of Medicine.
L. LAHUT UZMAN, M.D., (by invitation), Boston.
Associate in Neurology, Harvard Medical School.

New and occasionally toxic drugs, new and frequently toxic chemicals, and recent advances in the importance of copper, magnesium, and certain amino acids in relation to clinical neurology will be the starting point for this panel. It will then proceed to consider the diagnostic and therapeutic implications of some of the more common nutritional, metabolic, and toxic disorders of the nervous system.

THE CLINIC SESSIONS

Color Television of Medical Clinics

Between 9:00 A.M. and 11:00 A.M. each day, Tuesday through Friday, clinics presented at the New England Deaconess Hospital will be transmitted by closed circuit colored television to the Paul Revere Hall and Talbot Hall in Mechanics' Building. Members of the staffs of various hospitals are participating in producing the clinics and the wide range of subjects presented by authoritative clinicians insures a valuable as well as an interesting program.

The popularity of colored television in medical education is established and this important feature of our program is made possible through the sponsorship of the Smith, Kline and French Laboratories of Philadelphia. The College is also deeply indebted to the New England Deaconess Hospital for the use of its facilities in televising the clinics.

Admission by regular badge; no special tickets required.

Paul Revere and Talbot Halls

Mechanics' Building

Tuesday, April 9, 1957

Moderator: ALEXANDER MARBLE

A.M.

9:00– 9:20 Goiter, Myxedema and Iodine.

GEORGE O. BELL, Lahey Clinic.

A brief review of the subject of goiter and myxedema in relation to prolonged iodide ingestion.

9:20– 9:50 Ovarian Function After the Menopause.

HENRY M. LEMON, Massachusetts Memorial Hospitals.

Clinical and biochemical evidence will be presented indicating that ovarian stroma may secrete estrogen following induced or spontaneous menopause. The importance of ovarian conservation in benign disease will be stressed, as well as the role of oophorectomy, up to 70 years of age, as palliation for cancers of the breast. The role of oophorectomy as part of medical adrenalectomy using cortisone and prednisone for advanced mammary cancer will be emphasized.

9:50–10:10 Oral Hypoglycemic Agents in the Treatment of Diabetes.

ROBERT F. BRADLEY and LEO P. KRALL, Joslin Clinic and New England Deaconess Hospital.

Summary of the current status of blood sugar lowering agents administered by the oral route. Principal results concern the role of BZ55 and Orinase, but some preliminary data concerning still newer agents may by then require some comment. Major emphasis on clinical usefulness to date and selection of patients, toxicity, and potential long-range pitfalls.

10:10–10:40 Disorders of Calcium Metabolism.

PHILIP H. HENNEMAN, Massachusetts General Hospital.

Demonstration of two patients with disorders of calcium metabolism.

10:40–11:00 The Preservation of Platelets: Their Use in Transfusions and Antibody Tests.

JAMES L. TULLIS, New England Deaconess Hospital.

An apparatus permitting direct recovery of platelets during blood collection will be demonstrated. The isolated platelets will then be preserved and techniques shown for their later transfusion into patients and *in vitro* use in the performance of platelet agglutinin tests.

Wednesday, April 10, 1957

Moderator: C. CABELL BAILEY

A.M.

9:00– 9:20 Management of Urinary Tract Infections.

EDWARD H. KASS, Boston City Hospital.

Statement of recent advances in the bacteriologic diagnosis of infections of the urinary tract and of the frequency with which asymptomatic bacteriuria exists in the general population. The relevance of bacteriuria to the pyelonephritis problem will be discussed. The management of urinary tract infections will be discussed primarily from the point of view of the problem of individualization of therapy and the place of bladder rinse, suppressive nonantibiotic therapy and antibiotic therapy will be evaluated. Newer agents of potential usefulness will be discussed.

9:20– 9:50 Cardiac Resuscitation.

PAUL M. ZOLL, Beth Israel Hospital.

Resuscitation of the heart from ventricular standstill or ventricular fibrillation presents a critical emergency, often unexpected, in many different clinical situations. The technic of external electric stimulation of the heart can now be applied to resuscitate the heart from ventricular standstill. Similarly external countershock may be applied without the necessity of opening the chest to stop ventricular fibrillation. Cardiac resuscitation requires immediate recognition of the onset of arrest, the mechanism of the attack, and the immediate application of the appropriate electric current. For this purpose a cardiac monitor has been developed that does not require undivided attention but will signal the onset of arrest and will show the mechanism, standstill or fibrillation. To be most effective, cardiac resuscitation requires a three-fold approach of this nature.

9:50–10:10 Differential Diagnosis of the Arthritides.

FRANK P. FOSTER, Lahey Clinic.

Depending somewhat on the type of practice—osteoarthritis, rheumatoid arthritis and non-articular rheumatism (fibrositis, myositis, bursitis, etc.) constitute 80% to 90% of the common arthritic problems. Important diagnostic features of each will be covered.

Special mention is made of a newly recognized diagnostic problem; namely, the patient with rheumatoid arthritis who is or has been recently taking cortisone. A consultant unaware of this circumstance may find the common signs of the disease concealed and thus if not warned fail to make a correct diagnosis.

10:10–10:35 Clinical Application of Pulmonary Function Tests.

EDWARD A. GAENSLER, Thorndike Memorial Laboratory, Boston City Hospital.

Well standardized, generally useful methods for clinical evaluation of ventilatory function will be demonstrated and the significance of abnormal findings will be discussed in terms of disturbed mechanics of breathing. Several patients with various types of ventilatory insufficiency will be shown. Bronchospirometry will be demonstrated and indications and interpretations discussed. The role of tests for adequacy of intrapulmonary distribution of gases and for diffusion capacity measurements will be evaluated on the basis of clinical material. An attempt will be made to define the present place of pulmonary function studies in the practice of internal medicine.

10:35–11:00 Clinical Applications of Cardiac Catheterization.

JAMES A. BOUGAS, New England Deaconess Hospital, and WALTER T. GOODALE, Peter Bent Brigham Hospital.

Physiological and applied clinical examinations of cardiopulmonary function, including phonocardiography and both right and left heart catheterization, will be presented, carrying out as many of the actual procedures as possible.

Thursday, April 11, 1957

Moderator: ELMER E. HINTON

A.M.

9:00– 9:30 Present Clinical Applications of Vectorcardiography.

LOUIS WOLFF, Beth Israel Hospital.

The vectorcardiogram indicates the presence of certain conditions more clearly than does the electrocardiogram. Therefore, it has a definite use in the diagnosis of heart disease. The vectorcardiogram is of particular value in the diagnosis of right ventricular hypertrophy, right and left bundle branch block, inferior myocardial infarction, and acute cor pulmonale.

9:30–10:00 Rest in the Treatment of Myocardial Infarction.

SAMUEL A. LEVINE, Peter Bent Brigham Hospital.

A false conception prevails amongst the medical profession that the heart obtains its maximum rest with the patient in bed. There is clinical and physiological evidence to indicate that the work of the heart is less with the patient sitting in a chair with the feet down, than when recumbent in bed. What is more important is that cases of acute myocardial infarction generally do better both physically and psychologically and will have a lower immediate mortality with the chair treatment than with the bed treatment.

10:00–10:20—How to Get More Out of Your Laboratory Reports.

BRADLEY E. COPELAND, New England Deaconess Hospital.

The accuracy of clinical laboratory measurements is of great concern to all physicians. In order for clinicians to communicate with pathologists or other laboratory directors concerning the real significance of accuracy, an easily comprehended set of definitions of accuracy needs to be understood by both parties. There are a multitude of methods of expressing accuracy, most of which are confusing and difficult to interpret. The standard deviation will be presented as a method of expressing accuracy which is easy to understand and easy to calculate. A brief demonstration will also be given showing the fundamental basis for the standard deviation unit.

10:20–10:40 Clinical and Pathological Aspects of "Allergic" Vasculitis.

ROBERT P. MCCOMBS and JAMES F. PATTERSON, New England Center Hospital.

The clinical manifestations of "allergic" vasculitis are quite varied and may mimic those of the more clearly defined collagen diseases. Patients, photographs of lesions and photomicrographs of biopsy material will be shown and the general topic discussed.

10:40–11:00 Esophageal Washing for Cytology.

F. THOMAS GEPHART, Massachusetts General Hospital.

This subject will be our experience in over 250 esophageal washings in patients with both malignant and benign disease of the esophagus.

Friday, April 12, 1957

Moderator: THOMAS C. CHALMERS

A.M.

9:00– 9:30 Renal Transplants in Identical Twins.

WARREN R. GUILD, Peter Bent Brigham Hospital.

Three sets of identical twins have undergone renal homotransplantation. Data will be presented to contrast pre-transplant and post-transplant studies on the renal functional integrity in both recipient and donor twins. Application of the principles of renal transplantation in identical twins to renal transplantation among non-identical individuals will be discussed briefly.

9:30–10:00 Adrenalectomy and Hypophysectomy for Metastatic Malignancy of the Breast.

ELMER C. BARTELS and CHARLES A. FAGER, Lahey Clinic.

Clinical experience with 16 cases of metastatic breast malignancy after adrenalectomy and 7 cases after hypophysectomy.

10:00–10:30 Differential Diagnosis of Tremors.

DEREK E. DENNY-BROWN, Boston City Hospital.

Demonstration of patients with various types of tremor.

10:30–11:00 Selection and Training of Hemiparetics.

WILLIAM H. TIMBERLAKE and WESLEY G. WOLL, JR., Lemuel Shattuck Hospital.

Demonstration of techniques and tests used to select hemiparetic patients for rehabilitation training. Discussion of the relative merits of these procedures, and their role in the overall rehabilitation of the patients. Intended to point out the detrimental as well as the important positive findings and the important role of motivation in helping to achieve success. Patients will be presented to demonstrate the techniques of joint mobilization, wheelchair activitives, gait training with and without braces, and occupational therapy in functional training and activities of daily living.

THE CLINIC SESSIONS

Clinics at Hospitals

On Tuesday, April 9, and Thursday, April 11, 1957, from 9:00 to 11:00 A.M., clinics will be presented at various Boston hospitals. The geographical nearness of the hospitals to the Headquarters minimizes the time involved in transportation. Bus transportation has been arranged by the local Committee on Transportation starting from the Hotel Statler at 8:30 A.M. on these mornings and returning from the hospitals at 11:00 A.M. Bus tickets should be procured at the Registration Desk, Mechanics' Building, on the preceding day to insure adequate facilities. (Please consult the Section on "Transportation" for routing of the buses.)

Admission to the Hospital Clinics will require special tickets. Member registration blanks for the clinics are sent to all members with the program and should be filled out and returned to the Executive Secretary promptly. Upon receipt at the College Office, proper tickets will be selected and held at the Registration Bureau, Mechanics' Building, or, on request, will be mailed to the member. **Reservations by**

mail cannot be made after March 18, but tickets may be obtained in person at the Registration Bureau on the afternoon preceding any clinic day, provided space is still available. Non-members may procure tickets directly at the Registration Bureau depending upon availability.

Members who reserve clinic tickets are urgently requested to notify the Executive Secretary, and to return their tickets, if they find they will be unable to attend.

The Committee on Clinics has provided a wide range of medical topics for presentation—all illustrated by the demonstration of patients and all stressing the clinical application of the subject matter under discussion. In addition to the clinical sessions offered at the hospitals, a symposium on endocrine physiology is to be presented on Tuesday at the Harvard Medical School.

PROGRAM OF HOSPITAL CLINICS

Tuesday, April 9, 1957, 9:00–11:00 A.M.

A-1 BOSTON CITY HOSPITAL

818 Harrison Avenue

Dowling Amphitheatre

(Capacity 200)

MAXWELL FINLAND, Moderator

1. **Use of Steroids in Overwhelming Infections.**
   EDWARD H. KASS.
2. **Some Aspects of Adreno-cortical Disease.**
   ISADORE N. ROSENBERG.
3. **Thyroidal-ovarian Relationships.**
   NORBERT FREINKEL.

B-1 BETH ISRAEL HOSPITAL

330 Brookline Avenue

Sherman Auditorium

(Capacity 200)

HERRMAN L. BLUMGART, Moderator

1. **Emergency Cardiac Resuscitation: Demonstration of External Electric Pacemaker and Defibrillator.**
   PAUL M. ZOLL and ARTHUR J. LILENTHAL.
2. **Demonstration of a New In Vitro Test for the Clinical Evaluation of Thyroid Function. Case presentation.**
   A. STONE FREEDBERG and MILTON W. HAMOLSKY.
3. **Practical Management of Cardiac Patients Following RAI Induced Hypothyroidism. Case presentation.**
   HERRMAN L. BLUMGART and GEORGE S. KURLAND.
4. **The Use of Oral Preparations in the Treatment of Diabetes Mellitus. Case presentation.**
   SAMUEL B. BEASER.

D-1 MASSACHUSETTS GENERAL HOSPITAL

Fruit Street

Lower Outpatient Amphitheatre

(Capacity 120)

WALTER BAUER, Moderator

A.M.

9:00–10:00 **The Connective Tissue Diseases.**
WALTER BAUER and Associates.

CHESTER M. JONES, Moderator

10:00–11:00 **Malabsorption Syndromes.**
CHESTER M. JONES and Associates.

E-1 MASSACHUSETTS MEMORIAL HOSPITALS

750 Harrison Avenue

Evans 8 Amphitheatre

(Capacity 72)

ROBERT W. WILKINS, Moderator

1. **Differential Diagnosis and Treatment of Renal Disease.**
   ARNOLD S. RELMAN.
2. **The Treatment of Hyperthyroidism with Radioactive Iodine.**
   BELTON A. BURROWS.
3. **The Management of Hypertension.**
   ROBERT W. WILKINS.

F-1 NEW ENGLAND CENTER HOSPITAL

171 Harrison Avenue

Stearns Auditorium

(Capacity 100)

JOSEPH M. HAYMAN, JR., Moderator

A.M.

9:00 **Vasculitis.**
ROBERT P. MCCOMBS.

9:40 **Indications for Splenectomy.**
WILLIAM DAMESHEK.

10:20 **Changes in the Skin in Systemic Disease.**
JAMES F. PATTERSON.

G-1 PETER BENT BRIGHAM HOSPITAL

721 Huntington Avenue

Brigham Amphitheatre

(Capacity 239)

C. SIDNEY BURWELL, Moderator

1. **Pickwickian Syndrome.**
   C. SIDNEY BURWELL and Associates.
2. **Renal Failure.**
   JOHN P. MERRILL and Associates.

H-1 **VETERANS ADMINISTRATION HOSPITAL, Boston**

150 South Huntington Avenue

Auditorium E-3-109

(Capacity 100)

MAURICE B. STRAUSS, Moderator

1. **Hypopituitarism Associated with Hemochromatosis.**
   SOLOMON PAPPER.
2. **Milk-Alkali Syndrome versus Hyperparathyroidism.**
   MAURICE B. STRAUSS.
3. **Usefulness of the Schilling Test in the Etiological Diagnosis of Anemias.**
   AARON MILLER.
4. **Use of Radioiodine in the Diagnosis of Thyroid Disease.**
   D. WARD SLINGERLAND.

HMS **HARVARD MEDICAL SCHOOL**

25 Shattuck Street

Amphitheatre, Building D

(Capacity 245)

ROY O. GREEP, S.M., Ph.D., Professor of Anatomy and Dean, Harvard School of Dental Medicine, Moderator

SYMPOSIUM

"Recent Advances in Endocrinology"

In this symposium Dr. Greep and his Associates of the Faculty of the Harvard Medical School will present recent basic investigative work on endocrine physiology which promises to be of significant importance in its application to clinical endocrinology.

Thursday, April 11, 1957, 9:00–11:00 A.M.

A-2 **BOSTON CITY HOSPITAL**

818 Harrison Avenue

Dowling Amphitheatre

(Capacity 200)

WILLIAM B. CASTLE, Moderator

1. **Nutritional Deficiency Anemias: Hemolytic Anemias.**
   WILLIAM B. CASTLE and JAMES H. JANDL.

2. **Ferrokinetic Studies in Anemia.**
   JANE F. DESFORGES.

3. **Myeloproliferative Disorders.**
   WILLIAM C. MOLONEY.

B-2 **BETH ISRAEL HOSPITAL**

330 Brookline Avenue

Sherman Auditorium

(Capacity 200)

BENJAMIN ALEXANDER, Moderator

1. **Problems in the Evaluation of Male Gonadal Function. Case presentation.**
   PHILIP TROEN.

2. **The Medical and Surgical Aspects of Regional Enteritis.**
   LOUIS ZETZEL and JACOB FINE.

3. **Bleeding and Clotting.**
   One case of hemorrhagic disease.
   ROBERT GOLDSTEIN.
   One case of thrombotic disease with demonstration of method for prolonged intermittent intravenous therapy.
   STANFORD WESSLER.

C-2 **CHILDREN'S HOSPITAL**

300 Longwood Avenue

Jimmy Fund Auditorium

(Capacity 350)

CHARLES A. JANEWAY, Moderator

1. **Diagnostic and Therapeutic Aspects of Pancreatic Fibrosis.**
   HARRY SHWACHMAN.

2. **The Relationship of Varicella and Herpes Zoster.**
   THOMAS H. WELLER.

3. **Gamma Globulin and Protein Deficiencies, Congenital and Acquired.**
   DAVID GITLIN.

4. **The Danger of Aplastic Crises in Hemolytic Anemia.**
   LOUIS K. DIAMOND.

D-2 **MASSACHUSETTS GENERAL HOSPITAL**

Fruit Street

Lower Outpatient Amphitheatre

(Capacity 120)

PAUL D. WHITE, Moderator

1. **Longevity. Presentation of a patient, age 106.**
   PAUL D. WHITE.

2. **Successful Removal of Myxoma of the Left Atrium.**
   Edward F. Bland and J. Gordon Scannell.
3. **The Modern Management of Hypertension.**
   Robert S. Palmer.
4. **Reconstructive Vascular Surgery in the Treatment of Degenerative Arterial Disease.**
   Robert S. Shaw.
5. **Angiocardiography.**
   Stanley M. Wyman.

E-2 MASSACHUSETTS MEMORIAL HOSPITALS

750 Harrison Avenue

Evans 8 Amphitheatre

(Capacity 72)

Chester S. Keefer, Moderator

1. **The Differential Diagnosis and Treatment of Obstructive Pulmonary Disease.**
   Francis C. Lowell.
2. **Management of Bacterial Meningitis.**
   Louis Weinstein.
3. **The Management of Osseous Metastasis.**
   Henry M. Lemon.

F-2 NEW ENGLAND CENTER HOSPITAL

171 Harrison Avenue

Stearns Auditorium

(Capacity 100)

Samuel Proger, Moderator

A.M.

9:00 **Pyelonephritis.**
   Joseph M. Hayman, Jr.

9:40 **Unusual Disturbances of Electrolyte Balance.**
   William B. Schwartz.

10:20 **Management of Nodules in the Thyroid.**
   Edwin B. Astwood.

G-2 PETER BENT BRIGHAM HOSPITAL

721 Huntington Avenue

Brigham Amphitheatre

(Capacity 239)

GEORGE W. THORN, Moderator

1. Studies on Aldosterone.
GEORGE W. THORN and Associates.

2. Cardiac Clinic.
LEWIS DEXTER and Associates.

J-2 ROBERT BRECK BRIGHAM HOSPITAL

125 Parker Hill Avenue

Day Room

(Capacity 40)

THEODORE B. BAYLES, Moderator

A.M.

9:00–10:00 **Rheumatoid Arthritis: Medical and Orthopedic Treatment.**
J. SYDNEY STILLMAN, THEODORE B. BAYLES and THEODORE A. POTTER.

10:00–10:30 **Modern Management of Gout.**
VICTOR G. BALBONI and THEODORE B. BAYLES.

10:30–11:00 **Juvenile Rheumatoid Arthritis (Still's Disease).**
ROBERT E. BARKIN, VICTOR G. BALBONI and J. SYDNEY STILLMAN.

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Lindsay, J. R.: The Practical Management of Dizziness, California Med. 83:193 (Sept.) 1955.



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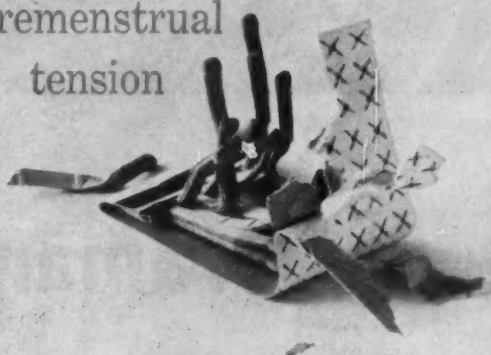
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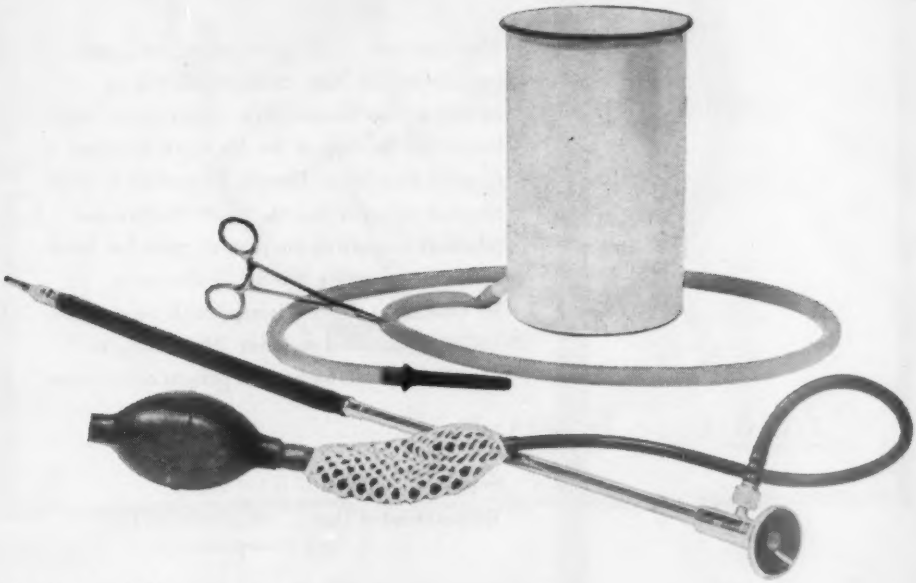
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This extensive study[1] gives additional insight into the role of high cholesterol levels in cardiovascular disease. In a recent paper,[2] read before the Meeting of the Michigan Academy of General Practice in Detroit, November 7, 1956, Sherber reported that the most effective and practical therapy in the past 15 years has been aimed at correcting this metabolic error. He concluded that: "Therapy with polysorbate 80-choline-inositol complex [MONICHOL] is practical and allows for full patient cooperation."

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1. Joint Report of the Technical Group of the Committee on Lipoproteins and Atherosclerosis (Gofman, J.W., et al.) and the Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council (Andrus, E.C., et al.): Circulation *14*:691 (Oct.) 1956.
2. Sherber, D.A.: Paper read before the Meeting of the Michigan Academy of General Practice, Detroit, Nov. 7, 1956.

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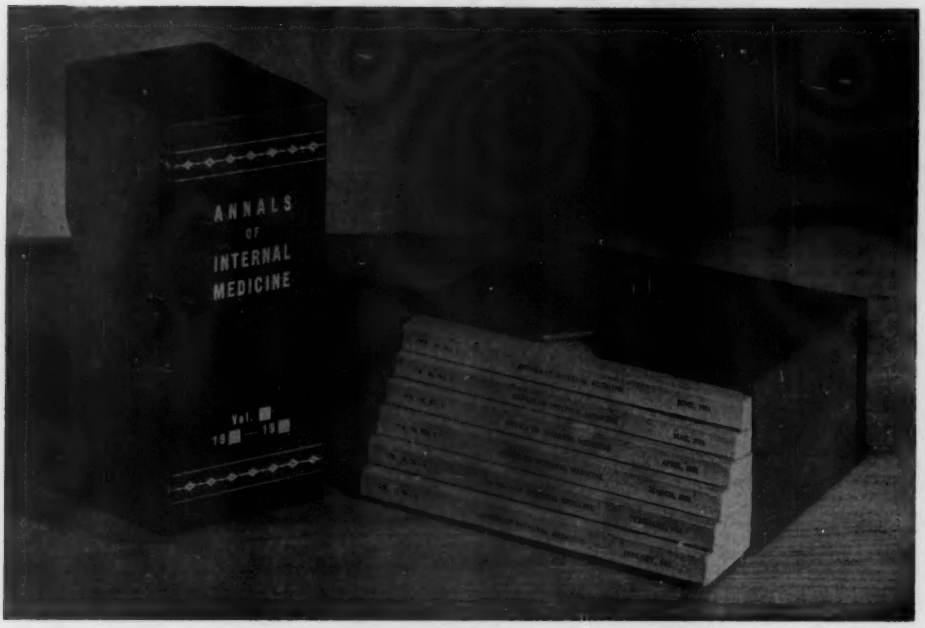
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Course No. 1, PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: The Frank E. Bunts Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director.				X													
Course No. 2, GASTRO-ENTEROLOGY: Boston University School of Medicine, Boston, Mass.; Franz J. Ingelfinger, M.D., F.A.C.P., Director.					X												
Course No. 3, INTERNAL MEDICINE: The University of Chicago Department of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director, and Robert G. Page, M.D., Co-director.											X						
Course No. 4, EARLY DETECTION AND PREVENTION OF DISEASE: University of Pennsylvania School of Medicine, Department of Public Health and Preventive Medicine, Philadelphia, Pa.; John P. Hubbard, M.D., F.A.C.P., and Norbert J. Roberts, M.D., F.A.C.P., Co-directors.												X					
Course No. 5, INTERNAL MEDICINE: Louisiana State University School of Medicine, Postgraduate Division, Shreveport, La.; Edgar Hull, M.D., F.A.C.P., and Marion D. Hargrove, M.D., F.A.C.P., Co-directors.												X					
Course No. 6, CARDIOLOGY: The National Institute of Cardiology of Mexico, Mexico, D. F.; Ignacio Chávez, M.D., F.A.C.P., Director.													X				
Course No. 7, INTERNAL MEDICINE: New York University Post-Graduate Medical School, New York, N. Y.; Charles F. Wilkinson, Jr., M.D., F.A.C.P., and Clarence E. de la Chapelle, M.D., F.A.C.P., Co-directors.													X				
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1. Best & Taylor, The Physiological Basis of Medical Practice, 6th Ed.

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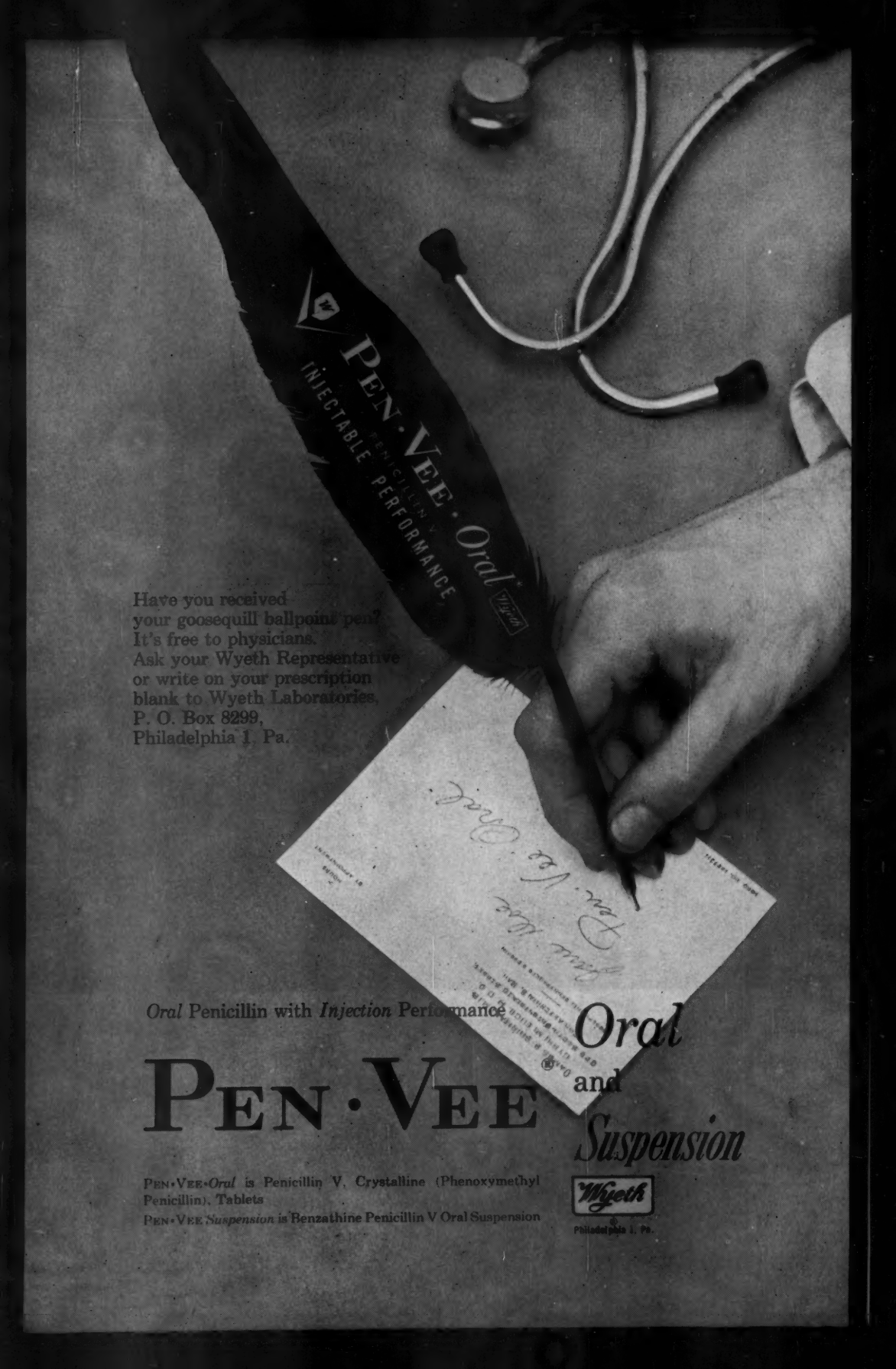
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1. Derome, L. Canad. M. A. J. 69:532, 1953.
2. Hardin, J. H., et al. South. M. J. 47:1190, 1954.

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[1]Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. *11*:1105.

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(1) Bauer, H. G., and Reckendorf, H. K.: A Study of the Soporific and Sedative Effectiveness of a Cycloheptenyl-ethylbarbiturate, New York State J. Med., to be published. (2) Brusca, D. D.: Clinical Study of Cycloheptenyl-ethylbarbiturate (Medomin) for Insomnia, J. Nerv. & Ment. Dis. *121*:67, 1955. (3) Fazekas, J. F., and Koppanyi, T.: The Effects of Cycloheptenylethyl Barbituric Acid (Medomin) in Man, to be published. (4) Koppanyi, T.; Morgan, C. F., and Princiotto, J. V.: Essential Elimination of Sodium Cycloheptenyl-ethylbarbiturate (Medomin) in Rabbits, J. Am. Pharm. A. (Scient. Ed.) *44*:221, 1955.

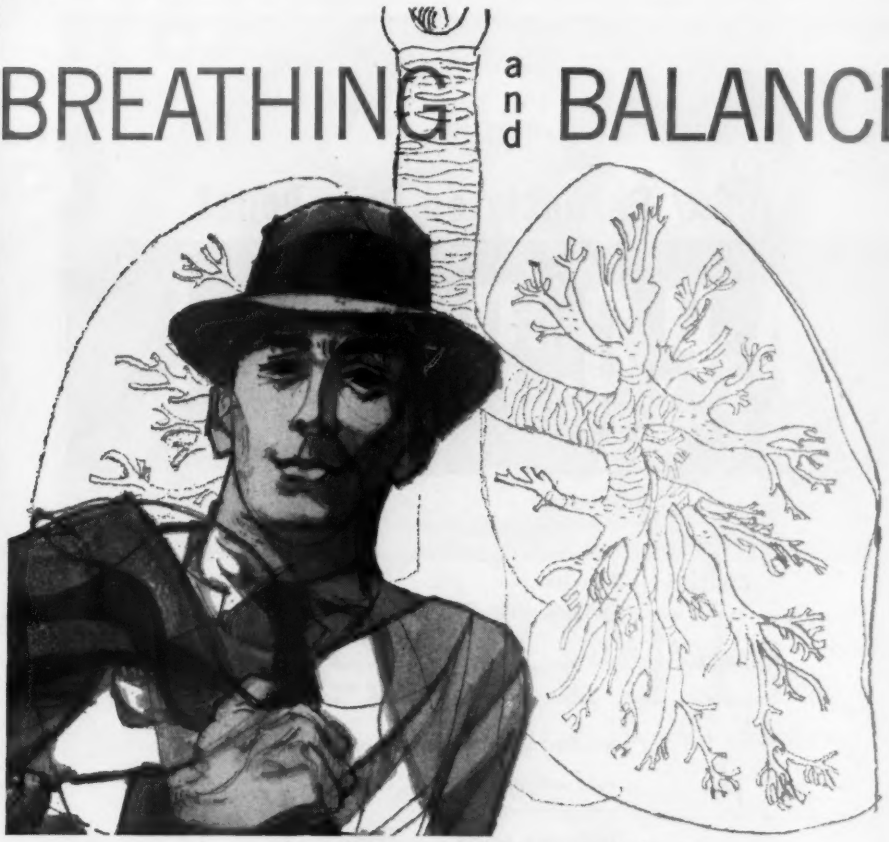
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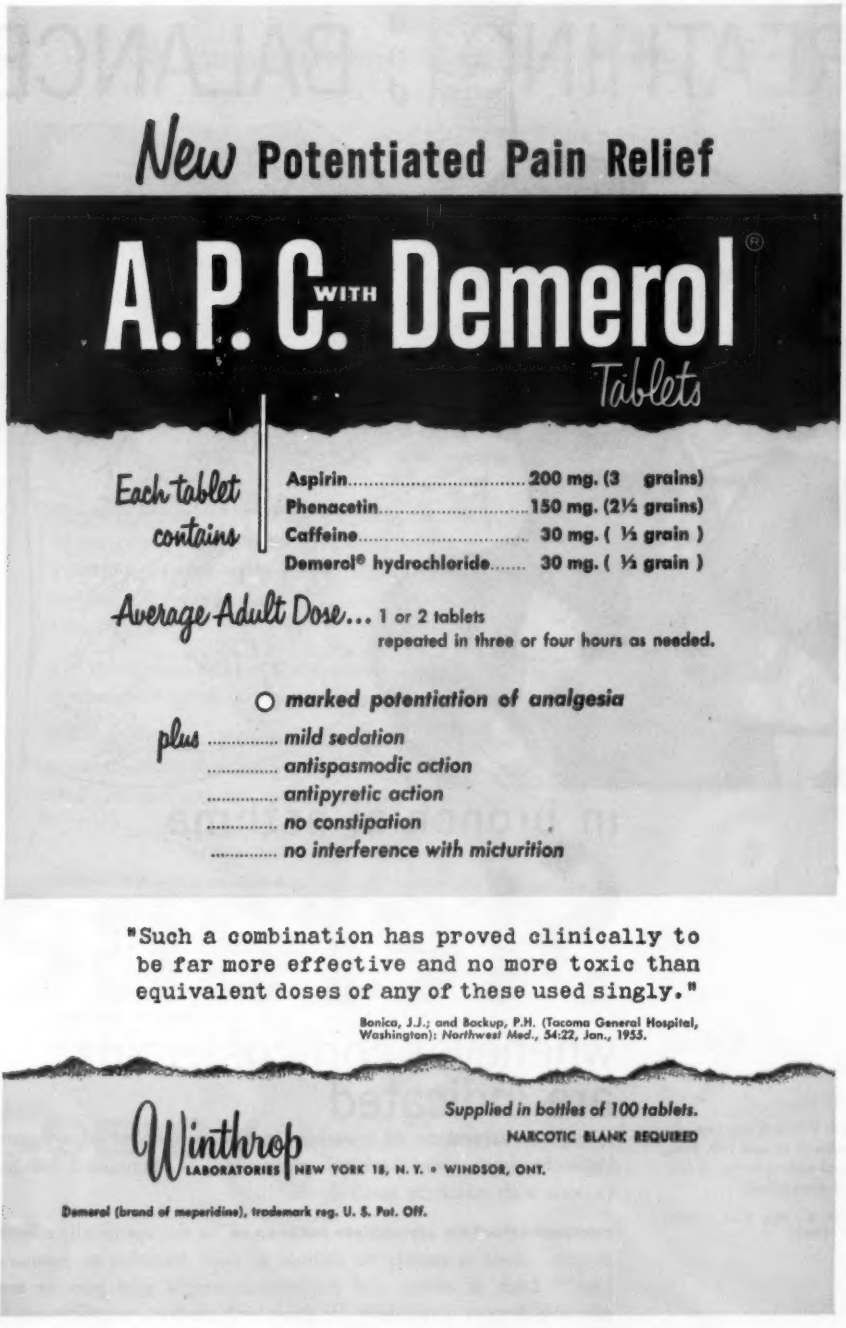
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*Schwartz, E.: New York J. Med. 56:570, 1956.

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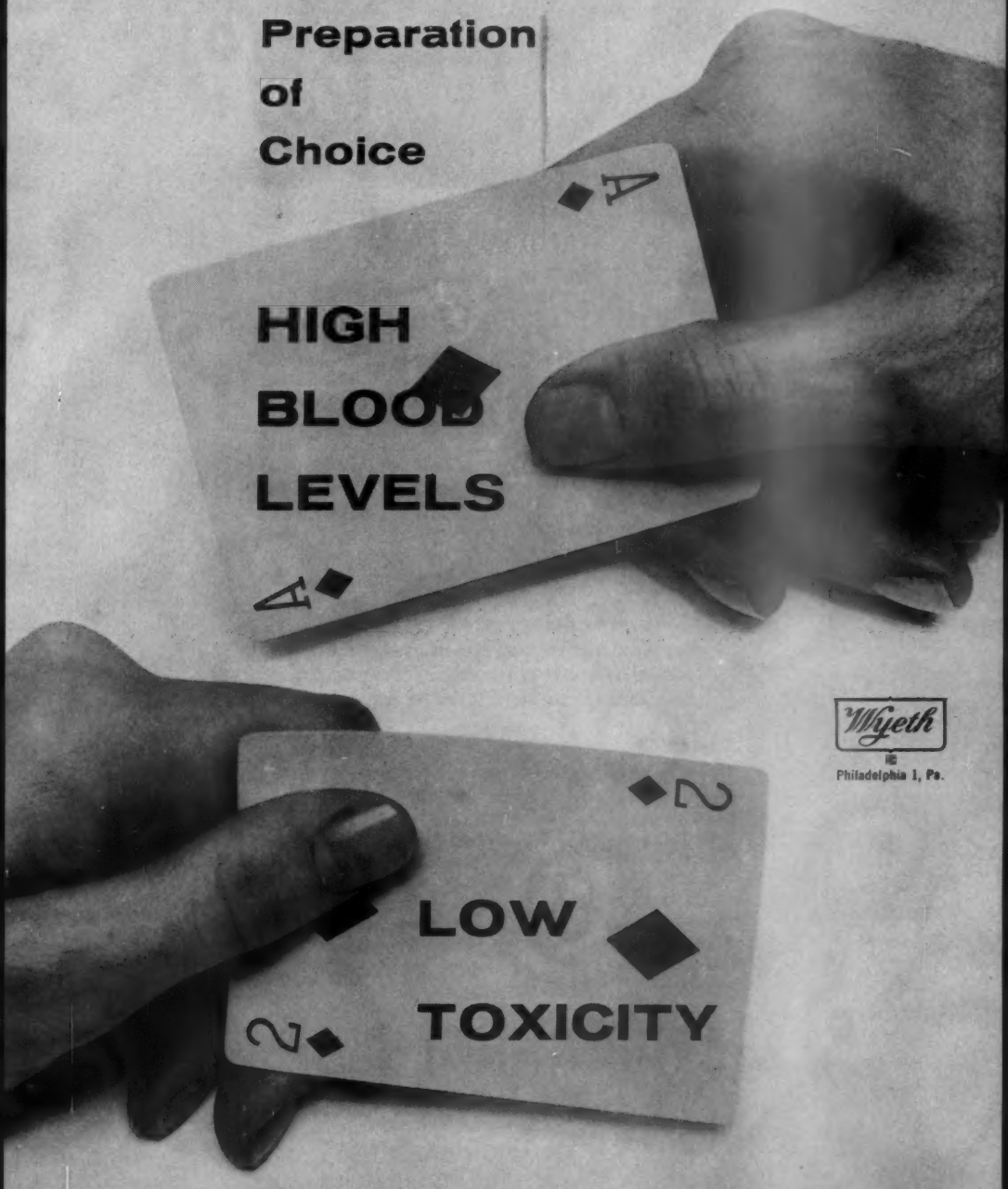
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